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D STAT QUE L33

=> d his full (FILE 'HOME' ENTERED AT 09:30:05 ON 11 OCT 2007) FILE 'REGISTRY' ENTERED AT 09:30:15 ON 11 OCT 2007 L1STRUCTURE UPLOADED 1 SEA SSS SAM L1 L2D SCA 560 SEA SSS FUL L1 L3 SAVE TEMP L3 LAO058STR1L/A FILE 'ZCAPLUS' ENTERED AT 09:35:51 ON 11 OCT 2007 L4117 SEA ABB=ON PLU=ON L3 L5 ANALYZE PLU=ON L4 1- RN : 5098 TERMS D D 1-20 FILE 'REGISTRY' ENTERED AT 09:37:09 ON 11 OCT 2007 L6 1 SEA ABB=ON PLU=ON 152044-54-7 1 SEA ABB=ON PLU=ON 152044-53-6 L7 1 SEA ABB=ON PLU=ON 189453-10-9 L8 1 SEA ABB=ON PLU=ON 186692-73-9 1 SEA ABB=ON PLU=ON 187527-25-9 1 SEA ABB=ON PLU=ON 188730-08-7 1 SEA ABB=ON PLU=ON 20949-84-2 1 SEA ABB=ON PLU=ON 106921-60-2 1 SEA ABB=ON PLU=ON 193146-27-9 0 SEA ABB=ON PLU=ON (L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14) AND L4 1 SEA ABB=ON PLU=ON 186692-73-9 L9 L10 L11 L12 L13L14 L15 OR L13 OR L14) AND L4 L16 0 SEA ABB=ON PLU=ON (L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14) AND L3 1 SEA ABB=ON PLU=ON 186692-84-2 L26 L27 O SEA ABB=ON PLU=ON L3 AND (L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26) L28 191 SEA ABB=ON PLU=ON L3 AND CASREACT/LC FILE 'ZCAPLUS' ENTERED AT 09:43:45 ON 11 OCT 2007 115 SEA ABB=ON PLU=ON L3/P L29 FILE 'CASREACT' ENTERED AT 09:53:42 ON 11 OCT 2007 L30 69 SEA ABB=ON PLU=ON L3 L31 STRUCTURE UPLOADED 0 SEA SUB=L30 SSS SAM L31 (0 REACTIONS) L32 23 SEA SUB=L30 SSS FUL L31 (468 REACTIONS) L33

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SN 10/563058 Page 168 of 172 STIC STN SEARCH RESULTS
     FILE 'REGISTRY' ENTERED AT 11:21:02 ON 11 OCT 2007
         22933 SEA ABB=ON PLU=ON OC15/ESS
L34
L35
          27330 SEA ABB=ON PLU=ON C16/ESS
           726 SEA ABB=ON PLU=ON NC15/ESS
L36
             O SEA ABB=ON PLU=ON NSC14/ESS
L37
          50989 SEA ABB=ON PLU=ON (L34 OR L35 OR L36 OR L37)
L38
L39
         12165 SEA ABB=ON PLU=ON L38 AND CASREACT/LC
     FILE 'CASREACT' ENTERED AT 11:22:32 ON 11 OCT 2007
          2534 SEA ABB=ON PLU=ON L39/PRO
L40
            59 SEA ABB=ON PLU=ON L30 (L) L40
L41
            65 SEA ABB=ON PLU=ON L3/RRT
L42
L43
            59 SEA ABB=ON PLU=ON L42 (L) L40
L44
            19 SEA ABB=ON PLU=ON L43 AND L33
    "FILE 'CAPLUS' ENTERED AT 11:34:47 ON 11 OCT 2007
           59 SEA ABB=ON PLU=ON L43
            53 SEA ABB=ON PLU=ON L45 AND PY<2005
L46
            49 SEA ABB=ON PLU=ON L45 AND PY<2004
L47
    FILE 'CASREACT' ENTERED AT 11:35:34 ON 11 OCT 2007
               D L43
            59 SEA ABB=ON PLU=ON L43 AND 1/NS
            50 SEA ABB=ON PLU=ON L43 AND 2/NS
L49
            44 SEA ABB=ON PLU=ON L43 AND 3/NS
L50
L51
            42 SEA ABB=ON PLU=ON L43 AND 4/NS
             9 SEA ABB=ON PLU=ON L48 NOT L49
L52
               D SCA
    FILE 'CAPLUS' ENTERED AT 11:45:06 ON 11 OCT 2007
L53
            45 SEA ABB=ON PLU=ON L45 AND J/DT
            14 SEA ABB=ON PLU=ON L45 AND P/DT
L54
           12 SEA ABB=ON PLU=ON L54 AND PD<20040619
L55 .
           39 SEA ABB=ON PLU=ON L53 AND ED<20040619
L56
             6 SEA ABB=ON PLU=ON L53 NOT L56
L57
             2 SEA ABB=ON PLU=ON L54 NOT L55
L58
L59
             8 SEA ABB=ON PLU=ON (L57 OR L58)
               SEL AN
     FILE 'CASREACT' ENTERED AT 11:47:33 ON 11 OCT 2007
L60
             8 SEA ABB=ON PLU=ON ("142:134344"/AN OR "143:211773"/AN OR
               "143:422202"/AN OR "144:170808"/AN OR "145:271524"/AN OR
               "145:397261"/AN OR "146:229070"/AN OR "146:251631"/AN OR
               "2004:985335"/AN OR "2005:1154536"/AN OR "2005:1305128"/AN OR
               "2005:614221"/AN OR "2006:1337456"/AN OR "2006:641138"/AN OR
               "2006:66747"/AN OR "2006:805502"/AN)
            51 SEA ABB=ON PLU=ON L48 NOT L60
L61
            42 SEA ABB=ON PLU=ON L49 NOT L60
L62
L63
            36 SEA ABB=ON PLU=ON L50 NOT L60
            35 SEA ABB=ON PLU=ON L51 NOT L60
L64
    FILE 'CAPLUS' ENTERED AT 11:49:27 ON 11 OCT 2007
               E US2006-563058 /APPS
L65
             1 SEA ABB=ON PLU=ON US2006-563058 /AP
               D SCA
               SEL RN
    FILE 'REGISTRY' ENTERED AT 11:50:13 ON 11 OCT 2007
            55 SEA ABB=ON PLU=ON (130486-85-0/BI OR 152044-53-6/BI OR
L66
               152044-54-7/BI OR 185148-95-2/BI OR 220367-73-7/BI OR 220774-16
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-3/BI OR 220774-19-6/BI OR 220774-20-9/BI OR 220774-21-0/BI OR
                220774-22-1/BI OR 220774-23-2/BI OR 220774-57-2/BI OR 220774-58
                -3/BI OR 220774-59-4/BI OR 220774-60-7/BI OR 220774-61-8/BI OR
                220774-62-9/BI OR 220775-18-8/BI OR 220775-76-8/BI OR 289477-70
                -9/BI OR 289477-71-0/BI OR 289477-72-1/BI OR 289477-73-2/BI OR
                289477-74-3/BI OR 303154-55-4/BI OR 303154-56-5/BI OR 303154-57
                -6/BI OR 303154-58-7/BI OR 303154-59-8/BI OR 303154-60-1/BI OR
                305840-13-5/BI OR 823203-01-6/BI OR 823203-02-7/BI OR 823203-03
                -8/BI OR 823203-04-9/BI OR 823203-05-0/BI OR 823203-06-1/BI OR
                823203-07-2/BI OR 823203-08-3/BI OR 823203-09-4/BI OR 823203-10
                -7/BI OR 823203-11-8/BI OR 823203-12-9/BI OR 823203-13-0/BI OR
                823203-14-1/BI OR 823203-15-2/BI OR 823203-16-3/BI OR 823203-17
                -4/BI OR 823203-18-5/BI OR 823203-19-6/BI OR 823203-20-9/BI OR
                823203-23-2/BI OR 823203-24-3/BI OR 823203-25-4/BI OR 823203-27
                -6/BI)
L67
              2 SEA ABB=ON PLU=ON L66 AND L39
                D SCA
     FILE 'CAPLUS' ENTERED AT 11:50:53 ON 11 OCT 2007
L68
              1 SEA ABB=ON PLU=ON L67 AND L65
                D SCA
     FILE 'REGISTRY' ENTERED AT 11:54:40 ON 11 OCT 2007
                E EPOTHILONE C/CN
L69
              1 SEA ABB=ON PLU=ON EPOTHILONE C/CN
                D SCA
L70
              1 SEA ABB=ON PLU=ON EPOTHILONE D/CN
                D SCA
                D RN L67 1-2
     FILE 'CASREACT' ENTERED AT 11:56:56 ON 11 OCT 2007
L71
             21 SEA ABB=ON PLU=ON
                                   152044-54-7/PRO
L72
             14 SEA ABB=ON
                           PLU=ON
                                   152044-53-6/PRO
L73
              7 SEA ABB=ON
                            PLU=ON L42 (L) L71
L74
              7 SEA ABB=ON
                            PLU=ON
                                   L42 (L) L72
L75
             14 SEA ABB=ON
                           PLU=ON
                                   (L73 OR L74)
L76
             13 SEA ABB=ON
                           PLU=ON L75 NOT L60
     FILE 'CAPLUS' ENTERED AT 11:58:45 ON 11 OCT 2007
L77
             11 SEA ABB=ON PLU=ON L45 AND PY<2000
                SEL AN
     FILE 'CASREACT' ENTERED AT 12:00:01 ON 11 OCT 2007
L78
             11 SEA ABB=ON PLU=ON ("126:251010"/AN OR "127:108793"/AN OR
                "127:293040"/AN OR "128:101936"/AN OR "129:189151"/AN OR
                "131:199535"/AN OR "131:286299"/AN OR "131:31819"/AN OR
                "131:31829"/AN OR "131:351125"/AN OR "132:49832"/AN OR
              . "1997:206419"/AN OR "1997:430309"/AN OR "1997:665094"/AN OR
                "1997:787450"/AN OR "1998:378435"/AN OR "1999:176999"/AN OR
                "1999:372044"/AN OR "1999:383492"/AN OR "1999:444724"/AN OR
                "1999:606636"/AN OR "1999:819379"/AN)
L79
             11 SEA ABB=ON PLU=ON L78 AND L43
L80
                           PLU=ON
             16 SEA ABB=ON
                                   L79 OR L52
L81
              1 SEA ABB=ON PLU=ON
                                   L80 AND L73
L82
              1 SEA ABB=ON PLU=ON L80 AND L74
             27 SEA ABB=ON PLU=ON L52 OR L79 OR (L81 OR L82) OR L76
L83
             15 SEA ABB=ON
                           PLU=ON L61 NOT L63
L84
                D FHIT 7
L85
             59 SEA ABB=ON PLU=ON L43 (L) 1/NS
             45 SEA ABB=ON PLU=ON L43 (L) 2/NS
L86
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             37 SEA ABB=ON PLU=ON L43 (L) 3/NS
L87
             31 SEA ABB=ON PLU=ON L43 (L) 4/NS
L88
L89
             21 SEA ABB=ON PLU=ON L43 (L) 5/NS
             28 SEA ABB=ON PLU=ON L85 NOT L88
L90
    FILE 'CAPLUS' ENTERED AT 12:09:08 ON 11 OCT 2007
L91
            80 SEA ABB=ON PLU=ON KLAR U?/AU
           116 SEA ABB=ON PLU=ON BUCHMANN B?/AU
L92
           60 SEA ABB=ON PLU=ON SCHWEDE W?/AU
L93
           186 SEA ABB=ON PLU=ON SKUBALLA W?/AU
L94
           32 SEA ABB=ON PLU=ON L91 AND (L92 OR L93 OR L94)
68 SEA ABB=ON PLU=ON L92 AND (L93 OR L94)
L95
L96
           24 SEA ABB=ON PLU=ON L93 AND L94
L97
           25 SEA ABB=ON PLU=ON L95 AND (L96 OR L97)
           24 SEA ABB=ON PLU=ON L96 AND L97
L99
           24 SEA ABB=ON PLU=ON L98 AND L99
L100
             1 SEA ABB=ON PLU=ON L100 AND L43
L101
     FILE 'REGISTRY' ENTERED AT 12:11:27 ON 11 OCT 2007
     FILE 'CAPLUS' ENTERED AT 12:11:29 ON 11 OCT 2007
                D STAT QUE L100
                D IBIB ABS L100 1-24
                D IBIB ABS L100 8-24
L102
             24 SEA ABB=ON PLU=ON L91 AND L92 AND L93 AND L94
                D COST FULL
                D IBIB ABS L102 TOT
                D IBIB L102 10
                D IBIB L102 9
                D ABS L102 8
               D ABS L102 8
                D IBIB ABS L102 9-24
     FILE 'REGISTRY' ENTERED AT 12:16:30 ON 11 OCT 2007
     FILE 'CASREACT' ENTERED AT 12:16:34 ON 11 OCT 2007
                D STAT QUE L33
                D IBIB ABS FHIT L33 1-23
     FILE 'CASREACT' ENTERED AT 12:18:14 ON 11 OCT 2007
                D STAT QUE L90
                D IBIB ABS FHIT L90 1-28
              3 SEA ABB=ON PLU=ON L77 NOT L90
L103
              3 SEA ABB=ON PLU=ON L78 NOT L90
L104
     FILE 'CAPLUS' ENTERED AT 12:40:57 ON 11 OCT 2007
             21 SEA ABB=ON PLU=ON L45 AND PY<2001
L105
                SEL AN
     FILE 'CASREACT' ENTERED AT 12:41:26 ON 11 OCT 2007
             21 SEA ABB=ON PLU=ON ("126:251010"/AN OR "127:108793"/AN OR
L106
                "127:293040"/AN OR "128:101936"/AN OR "129:189151"/AN OR
                "131:199535"/AN OR "131:286299"/AN OR "131:31819"/AN OR
                "131:31829"/AN OR "131:351125"/AN OR "132:251011"/AN OR
                "132:49832"/AN OR "133:266631"/AN OR "133:266634"/AN OR
                "133:321737"/AN OR "133:362657"/AN OR "134:178371"/AN OR
                "134:29228"/AN OR "134:4795"/AN OR "134:56502"/AN OR "135:37156
                6"/AN OR "1997:206419"/AN OR "1997:430309"/AN OR "1997:665094"/
                AN OR "1997:787450"/AN OR "1998:378435"/AN OR "1999:176999"/AN
                OR "1999:372044"/AN OR "1999:383492"/AN OR "1999:444724"/AN OR
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FILE HOME

FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 10 OCT 2007 HIGHEST RN 950149-06-1 DICTIONARY FILE UPDATES: 10 OCT 2007 HIGHEST RN 950149-06-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

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FILE CONTENT: 1840 - 6 Oct 2007 VOL 147 ISS 16

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Some CASREACT records are derived from the ZIC/VINITI database (1974-1999) provided by InfoChem, INPI data prior to 1986, and Biotransformations database compiled under the direction of Professor Dr. Klaus Kieslich.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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http://www.cas.org/infopolicy.html

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FILE 'REGISTRY' ENTERED AT 11:21:02 ON 11 OCT 2007
22933 SEA AlB=ON PLU=ON OCI5/ESS
7330 SEA ABB=ON PLU=ON CI6/ESS
726 SEA ABB=ON PLU=ON NCI5/ESS
0 SEA ABB=ON PLU=ON NCI5/ESS
10599 SEA ABB=ON PLU=ON LI3/ESS
50999 SEA ABB=ON PLU=ON LI3/OR LI

726 SEA ABB=ON 0 SEA ABB=ON 50989 SEA ABB=ON 12165 SEA ABB=ON

DLJ=0N 139/PRO . PLJJ=0N 139/PRO . PLJJ=0N 139/PRO . PLJJ=0N 130 (L) L40 PLJJ=0N 13/RRT

PLU=ON
PLU=ON
PLU=ON
PLU=ON

CASRRACT' ENTERED A 2534 SEA ABB-ON PU 59 SEA ABB-ON PU 65 SEA ABB-ON PU 59 SEA ABB-ON PU 19 SEA ABB-ON PU

FILE

L42 (L) L40 L43 AND L33

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CASREACT ENTERED AT 11:35:34 ON 11 OCT 2007

D 1.43

L43 AND 1/NS L43 AND 2/NS L43 AND 3/NS L43 AND 4/NS L48 NOT L49

PLU-ON PLU-ON PLU-ON PLU-ON

59 SEA ABB=ON P 50 SEA ABB=ON P 44 SEA ABB=ON P 42 SEA ABB=ON P 9 SEA ABB=ON P

'CAPLUS'

FILE

**CAPLUS' ENTERED AT 11:34:47 ON 11 OCT 2007 59 SEA ABB—ON PLU—ON L43 ST SEA ABB—ON PLU—ON L45 AND PY-2005 49 SEA ABB—ON PLU—ON L45 AND PY-2004

FILE

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148
150
151
151
134
135
137
138
138
                                                                                                                                                                                                                                                                            22222
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 (L6 OR L7 OR L8 OR L9 OR L10 OR L11
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             (L6 OR L7 OR L8 OR L9 OR 1.10 OR L11
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         8 OR L18 OR 1
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  OR LIZ OR LI3 OR LI4 OR LI5 OR LI6 OR LI7 OR LOS OR LZ1 OR LZ2 OR LZ3 OR LZ4 OR LZ5 OR LZ6) SEA ABB=ON: PLU=ON L3 AND CASREACT/LC
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      REACTIONS)
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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           5098 TERMS
                                                                                                                                                                    FILE 'REGISTRY' ENTERED AT 09:30:15 ON 11 OCT 2007
STRUCTURE UPLOADED
1 SEA SSS SAM L1
D SCA
560 SEA SSS FUL L1
SAVE TEMP L3 LA0058STR1L/A
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    FILE 'REGISTRY' ENTERED AT 09:37:09 ON 11 OCT 2007
                                                                                                                                                                                                                                                                                                                                                                                                                    FILE 'ZCAPLUS' ENTERED AT 09:35:51 ON 11 OCT 2007
117 SEA ABB=ON PLU=ON L3
ANALYZE PLU=ON L4 1- RN : 5098 TER
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              'ZCAPIUS' ENTERED AT 09:43:45 ON 11 OCT 2007 115 SEA ABB=ON! PIU=ON L3/P
                                                                                                       (FILE 'HOME' ENTERED AT 09:30:05 ON 11 OCT 2007)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      PLD=ON 184246-38-6
PLD=ON 189453-35-8
PLD=ON 219989-84-1
PLD=ON 63928-37-0
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 SEA ABB=ON PLU=ON 187283-46-1
SEA ABB=ON PLU=ON 188899-14-1
S S 184246-39-6
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    193146-27-9
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             OR L13 OR L14) AND L4
SEA ABB=ON PLU=ON (L6
OR L13 OR L14) AND L3
I SEA ABB=ON PLU=ON 1872
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         ABB=ON - PLU=ON
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                                              -> d his full
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L31
L32
L33
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55 SEA ABB-ON PLU-ON (130486-85-0/BI OR 152044-53-6/BI OR 152044-54-7/BI OR 185148-95-2/BI OR 220367-73-7/BI OR 220774-16
                                                                                                                                                                                                                                                                                                                 8 SEA ABB-ON PLU-ON ("142:13444"/AN OR "143:211773"/AN OR "143:42202"/AN OR "144:170808"/AN OR "145:2754"/AN OR "143:397261"/AN OR "146:22970"/AN OR "146:251631"/AN OR "16:229070"/AN OR "2005:61184538"/AN OR "2005:61184538"/AN OR "2005:611381"/AN OR "2006:66747"/AN OR "2006:6133456"/AN OR "2006:641138"/AN SEA ABB-ON PLU-ON L49 NOT L60 42 SEA ABB-ON PLU-ON L50 NOT L60 35 SEA ABB-ON PLU-ON L51 NOT L60 35 SEA ABB-ON PLU-ON L51 NOT L60
45 SEA ABB-ON PLU-ON L45 ND VDT 12 SEA ABB-ON PLU-ON L45 AND VDT 14 SEA ABB-ON PLU-ON L54 AND PVDT 12 SEA ABB-ON PLU-ON L54 AND PDC-20040619 39 SEA ABB-ON PLU-ON L53 AND EDC-20040619 6 SEA ABB-ON PLU-ON L53 ND L55 8 SEA ABB-ON PLU-ON L53 ND L55 8 SEA ABB-ON PLU-ON L57 NOT L56 SEA ABB-ON PLU-ON L57 NOT L55 8 SEA ABB-ON PLU-ON L57 OR L58) SEL AN
                                                                                                                                                                                                                                                                                                FILE 'CASREACT' ENTERED AT 11:47:33 ON 11 OCT 2007
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          'REGISTRY' ENTERED AT 11:50:13 ON 11 OCT 2007
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   'CAPLUS' ENTERED AT 11:49:27 ON 11 OCT 2007
E US2006-563058 /APPS
1 SEA ABB=ON PLU=ON US2006-563058 /AP
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155
156
158
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L62
L63
L64
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SN 10/563058 Page 165 of 172 STIC STN SEARCH RESULTS

• STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT •

RCT H 188730-19-0 RX (3) NGT J 4136-95-2 2,4,6-C13C6H2COC1, K 121-44-8 Et3N SOL 109-99-9 THF

STAGE(2) RGT L 1122-58-3 4-DMAP SOL 108-88-3 PhMe

THERE ARE 100 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT PRO I 186692-84-2 NTE key step REFERENCE COUNT: 100

SREACT COPYRIGHT 2007 ACS on STN 1 126:251010 CASREACT FULL-text Total synthesis of spothilone A: the macrolactonization approach 1, Nicolaou, K. C.; Sarabia, Francisco; Ninkovic, Sacha; L90 ANSWER 28 OF 28 CASREACT ACCESSION NUMBER: 126:25 TITLE: Total AUTHOR(S):

Yang, Zhen Dep: Chem., Skaggs Inst. Chem. Biol., Scripps Res. CORPORATE SOURCE:

Inst., La Jolle, CA, 92037, USA Angewendte Chemie, International Edition in English (1997), 36(5), 525-527 CODE: ACIENY, ISSN: 0570-0833

SOURCE:

VCH. Journal English PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

Me3CMe2SiO

Epothilone A (I) was prepared via a highly convergent and flexible route with macrolactonization of hydroxy acid II as the key step. 8

SN 10/563058 Page 166 of 172 STIC STN SEARCH RESULTS

<=== H RX(4) OF 4

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RCT M 188730-19-0 RX (4) STACE(1)
RGT 0 4136-95-2 2,4,6-C13C6H2COC1, P 121-44-8 Et3N
SOL 109-99-9 THF

RGT Q 1122-58-3 4-DMAP SOL 108-88-3 PhMe STAGE(2)

PRO N 186692-84-2 NTE key step 27 REFERENCE COUNT:

THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

SN 10/563058 Page 163 of 172 STIC STN SEARCH RESULTS

HIELD 758

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RCT G 201136-77-8 RX(2)

RGT I 4136-95-2 2,4,6-C13C6H2COC1, J 121-44-8 Et3N SOL 109-99-9 THF STAGE (1)

STAGE(2) RGT K 1122-58-3 4-DMAP SOL 108-88-3 PhMe

THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT 20. PRO H 201136-78-9. REFERENCE COUNT: 20.

127:293040 CASREACT Full-text
Total Syntheses of Epothilones A and B
Meng, Donglang's Bertinato, Peter; Balog, Aaron; Su,
Dai-Shi; Kamenecka, Ted; Sorensen, Eilk; Danishefsky, Samuel J. Leboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, New York, NY, 10021, Journal of the American Chemical Society (1997), CASREACT COPYRIGHT 2007 ACS on STN 119(42), 10073-10092 CODEN: JACSAT; ISSN: 0002-7863 American Chemical Society L90 ANSWER 27 OF 28 ACCESSION NUMBER: CORPORATE SOURCE: PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI TITLE: AUTHOR(S): SOURCE:

SN 10/563058 Page 164 of 172 STIC STN SEARCH RESULTS

Four distinct ring-forming strategies were pursued. Of these four, three were reduced to practice. In one approach, the action of a base on a substance possessing an acetate ester and a nonenolizable aldehyde brought about a remarkably effective macroaldolization simultaneously creating the C2-C3 bond and the hydroxyl-bearing stereocenter at C-3. Alternatively, the 16-membered macrolide of the epothilones could be fashioned through a C12-C13 ring-closing olderin metathesis and through macrolactonization of the appropriate hydroxy development of a novel cyclopropane solvolysis strategy for incorporating the diene-aldehyde cyclocondensation (LACDAC) and asym. allylation methodol. are permitted the establishment of a cis C12-C13 olefin, thus setting the stage acid. The application of a stereospecific B-alkyl Suzuki coupling strategy geminal Me groups of the epothilones, and the use of Lewis acid catalyzed for an eventual site- and diastereoselective epoxidn. reaction.

H cest I... RX(3) OF 59

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SN 10/563058 Page 161 of 172 STIC STN SEARCH RESULTS

RX(1) OF 1

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

RCT A 201136-77-8 RX (1)

STAGE(1) RGT C 121-44-8 Et3N, D 4136-95-2 2,4,6-Cl3C6H2COCl SOL 109-99-9 THF

STAGE (2) RGT E 1122-58-3 4-DWAP SOL 108-88-3 PhMe

PRO B 209260-71-9 REFERENCE COUNT: 40

THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L90 ANSWER 26 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 128:101936 CASREACT Full-text
TITLE: Total synthesis of 26-hydroxyepothilone B and related

Nicolaou, K. C.; Ninkovic, Sacha; Finlay, M. Ray V.;

Sarabia, Francisco; Li, Tianhu Department of Chemistry and Blochemistry, University California, California, 92093, USA

CORPORATE SOURCE:

SOURCE:

AUTHOR(S):

Chemical Communications (Cambridge) (1997), (24),

CODEN: CHCOFS; ISSN: 1359-7345 Royal Society of Chemistry 2343-2344

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

SN 10/563058 Page 162 of 172 STIC STN SEARCH RESULTS

A series of 26-substituted epothilones B, e.g. I, were constructed by total synthesis involving a selective Wittig olefination, an aldol reaction and a macrolactonization as key steps. 8

\ 0 0 0 0 b RX(2) OF 2

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AUTHOR(S):

methodology for the rapid, highly selective and convergent construction of epothilone ${\tt B}$

CORPORATE SOURCE:

SOURCE:

Nicolaou, K. C.; Hepworth, David; Finlay, M. Ray V.; Paul King, N.; Merschkun, Barbara; Bigot, Antony Department of Chemistry, The Skagas That. Cham. Biol., The Scripps Res. Inst., La Jolla, CA, 92037, USA Chemical Communications (Cambridge) (1999), (6), 519-520

CODEN: CHOOFS; ISSN: 1359-7345 Royal Society of Chemistry

English

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

During a synthesis of 16-desmethylepothilone B (1) new methods for the convergent and highly stereoselective synthesis of epothilone B and analogs were developed. Æ

ğ BI. ٠. AK RX(18) OF 37

ВК

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RCT BK 226940-48-3, BL 108-88-3 RX(18)

RGT BR 4136-95-2 2,4,6-Cl3C6H2COCl, BC 121-44-8 Et3N SOL 109-99-9 THF STAGE(1)

STAGE(2)

CAT 1122-58-3 4-DMAP SOL 108-88-3 PhMe

THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT BQ **226940-49-4** key step 13 REFERENCE COUNT: PRO

COPYRIGHT 2007 ACS on STN CASREACT L90 ANSWER 25 ÓF 28 ACCESSION NUMBER:

129:189151 CASREACT: Full-text
Total synthesis of 26-hydroxy-epothilone B and related
analogs via a macrolactonization based strategy
Nicolaou, K. C.; Finlay, M. Ray V.; Ninkovic, Sacha; Sarabia, Francisco CORPORATE SOURCE:

AUTHOR(S):

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037

Tetrahedron (1998), 54(25), 7127-7166 CODEN: TETRAB: ISSN: 0040-4020 Elsevier Science Ltd. PUBLISHER: SOURCE:

DOCUMENT TYPE: LANGUAGE: GI

The chemical synthesis of a series of 26-substituted epothilones B was described. Fully protected 26-hydroxydesoxy-epothilone B I (R = 51Me2CMe3), R1 = CPh3), prepared via a macrolactonization strategy, served as a common precursor to the designed epothilones described. The synthesized compds. were members of a large epothilone library of a number of antitumor agents. æ

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SN 10/563058 Page 157 of 172 STIC STN SEARCH RESULTS

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RCT T 241129-39-5 RX(4).

RGT V 84033-23-8 Benzoyl chloride, trichloro-, W 121-44-8 Et3N SOL 109-99-9 THF STAGE(1)

STAGE (2)

RGT X 1122-58-3 4-DWAP SOL 108-88-3 PhMe, 109-99-9 THF

PRO U **241129-40-8**REFERENCE COUNT: 12

THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

COPYRIGHT 2007 ACS on STN CASREACT Full-text 131:31829 CASREACT L90 ANSWER 23 OF 28 ACCESSION NUMBER:

A process for the preparation of ring-opened epothilone intermediates which are useful for the preparation of epothilone analogs

Kim, Soong-Hoon; Borzilleri, Robert M. Bristol-Myers Squibb Company, USA PCT Int. Appl., 20 pp. CODEN: PIXXD2 PATENT ASSIGNEE(S): INVENTOR (S):

Pațent English

DOCUMENT TYPE: LANGUAGE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

19981130 APPLICATION NO. KIND DATE WO 9927890 PATENT NO.

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19981130 19981013 US 1998-170582 CA 1998-2312098 EP 1998-960564 20020402 19990610 20000920

GB, GR, IT, LI, LU, NL, SE, MC, PT, 19981130 19981130 19981130 AU 1999-16134 JP 2000-522878 ZA 1998-10993 US 1997-67550P WO 1998-US25408 CH, DE, DK, ES, FR, 20011011 20030729 20000601 B2 R: AT, BE, IE, FI US 6365749 CA 2312098 EP 1035824 AU 739380 JP 2003522

MARPAT 131:31829 OTHER SOURCE(S): GI

PRIORITY APPIN. INFO.:

ZA 9810993

2003522722

19981201 19971204 19981130

SN 10/563058 Page 158 of 172 STIC STN SEARCH RESULTS

A process to produce ring opened epothilones (I) | [NRIR2 = N3, (un) substituted amine) and their use in the preparation of epothilone analogs (II) is presented. Thus, epothilone B is cleaved with NaN3, azide reduced to amine amine) and their use in the preparation of epothilone analogs (II) is presented. Thus, epothilone B is cleaved with NaN3, azide reduced to amine and macrolactamized with diphenylphosphoryl azide to give II in 40% yield. 2

^=== RX(3) OF 6

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

K 26386-88-9 (Pho)2P(O)N3 J 219989-84-1 RGT PRO SOL RX (3)

68-12-2 DME

Synthesis of 16-desmethylepothilone B: improved CASREACT COPYRIGHT 2007 ACS on STM 131:31819 CASREACT Full-text L90 ANSWER 24 OF 28 ACCESSION NUMBER: TITLE:

SN 10/563058 Page 155 of 172 STIC STN SEARCH RESULTS A <=== Q... RX(2) OF 215

PAGE 1-B

<u>3</u>

STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(2) RCT D 193146-51-9
PRO B 152044-54-7
NTE 11t. ref. . .
REFERENCE COUNT: 82

THERE ARE 82 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

CASREACT L90 ANSWER 22 OF 28 ACCESSION NUMBER: TITLE:

Harris, Christina R.; Kuduk, Scott D.; Balog, Aaron; Savin, Ken; Glunz, Peter W.; Danishefsky, Samuel J. SREACT COPYRIGHT 2007 ACS on STN
131:286299 CASREACT FULL-text
New Chemical Synthesis of the Promising Cancer
Chemcherapoutic Agent 12,13-Dasoxypochilone B:
Discovery of a Surprising Long-Range Effect on the
Disstereoselectivity of an Aldol Condensation

Sloan-Kettering Institute for Cancer Research, New

Laboratory for Bioorganic Chemistry, The

CORPORATE SOURCE:

AUTHOR(S):

155

SN 10/563058 Page 156 of 172 STIC STN SEARCH RESULTS

SOURCE:

Journal of the American Chemical Society (1999), 121(30), 7050-7062 , CODEN: JACSAT; ISSN: 0002-7863 American Chemical Society Journal English

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

remarkable ability to arrest cell division through the stabilization of microtubule assemblies. In vivo studies with 12,13-desoxyepothilone B (dEpoB) (1), have established that the desoxy compound is well tolerated and virtually methylpentenal moiety B (III), and the thiazoyl-containing vinyl iodide moiety C (IV). It was envisioned that a diasteroseslective aldol condensation between an achiral C5-C6 (2)-metalloenolate derived from construct A and an (S)-2-methylalkanal fragment, B, would generate the desired C6-C7 bond. Second, a B-alkyl Suzuki coupling between the vinyl iodide construct C and an alkyl borane would form the C11-C12 bond. Finally, a late-stage reduction of the C3 ketone to the requisite C3 alc. with high asym. induction would permit curative against a variety of sensitive and resistant xenograft tumors in animal models. In light of these discovaries, a chemical synthesis of dEpoB would be able to support a serious and substantial discovary research program directed toward the clin. development of this mol. The overall strategy for this endeavor assumed the ability to synthesize dEpoB from three constructs readily accessible achiral building block. The governing concepts the new introduction of the $\mathfrak{g},\delta ext{-diketo}$ ester fragment A, into the synthesis as a The epothilones are naturally occurring cytotoxic mols. that possess the which include an achiral β,δ -diketo ester construct A (II), an (S)-2æ

À I RX(4) OF 5

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The enantioselective total synthesis of epothilone A was achieved via the catalytic coupling of I and II. The key step in the preparation of I was the catalytic coupling of I and II. The key step in the preparation of I was t catalytic cyanosilylation of III. II was prepared via a catalytic organic acetalization followed by an aldol reaction. B.

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RCT C 188730-19-0 RX (5)

RGT AD 4136-95-2 2,4,6-C13C6H2COC1, AE 121-44-8 Et3N STAGE (1)

SN 10/563058 Page 154 of 172 STIC STN SEARCH RESULTS

SOL 109-99-9 THF

STAGE(2) RGT AF 1122-58-3 4-DMAP SOL 108-88-3 PhMe

AC 186692-84-2 41

PRO AC REFERENCE COUNT:

THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Schinzer, Dieter; Bauer, Armin; Schieber, Jennifer Chemisches Institut der Otto-von-Guericke-Universitat, Magdeburg, D-19106, Germany Chemistry--A European Journal (1999), 5(9), 2492-2500 CODEN: CEUJED; ISSN: 0947-6539 Wiley-VCH Verlag GmbH COPYRIGHT 2007 ACS on STN Syntheses of (-)-epothilone 131:351125 CASREACT Journal English CASREACT L90 ANSWER 21 OF 28 ACCESSION NUMBER: AUTHOR(S): CORPORATE SOURCE: PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI SOURCE:

acid. The first synthesis is based on our preceding paper. The critical trisubstituted double bond C12-13 in our second approach was constructed by a highly efficient Pd-mediated coupling reaction. Ring closure was achieved by scale to provide sufficient material for biol. tests. Thiazole fragment II (TBDMS = SIMe2CMe3) was obtained by an improved route starting from (S)-malic Two efficient routes for the total synthesis of (-)-epothilone B (I) are reported. One strategy is based on ring-closing metathesis, and a second synthesis on a macrolactonization. The key fragments are available on large highly efficient Pd-mediated coupling reaction. macrolactonization.

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STAGE(2)

SOL 141-78-6 ACOEt STAGE (3)

PRO

AL 219989-84-1
PHOSPHATE BUFFER USED INSECOND STAGE
NT:
80 THERE ARE 80 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT REFERENCE COUNT:

COPYRIGHT 2007 ACS on STN 6631 CASREACT . Full-text CASREACT L90 ANSWER 19 OF 28 ACCESSION NUMBER:

133:266631 CASREACT

Total Synthesis of Epothilone A AUTHOR(S): CORPORATE SOURCE:

Zhu, Bin, Panek, James S.
Department of Chemistry and the Center for Streamlined Synthesis Maccalf Center for Science and Engineering, Boston University, Boston, MA, 02215, USA organic Letters (2000), 2(17), 2575-2578

CODEN: ORLEF7; ISSN: 1523-7060

SOURCE:

American Chemical Society Journal English

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

like mechanism of action. A total synthesis of I is reported, which utilizer chiral silane-based bond construction methodol. to introduce the key G-6 and The C-15 stereocenter of fragment (III) was established by a lipase-mediated kinetic resolution. The fragments were assembled with a Suzuki coupling reaction and an aldol condensation and cyclized with a Yamaguchi-type macrolactonization reaction. Epothilones A (I) and B are potent antitumor natural products with a Taxolsynthesis of I is reported, stereocenters of fragment (II). æ

VH BE > RX(4) OF 6

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W YIELD 738

RCT V 297131-85-2 RX (4)

RGT X 4136-95-2 2,4,6-C13C6H2COC1, Y 121-44-8 Et3N SOL: 109-99-9 THF STAGE (1)

RGT Z 1122-58-3 4-DMAP SOL 108-88-3 PhMe STAGE (2)

W 297131-86-3 PRO NTE

THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT stereoselective 36 REFERENCE COUNT:

COPYRIGHT 2007 ACS on STN L90 ANSWER 20 OF 28 CASREACT ACCESSION NUMBER: 132:25

132:251011 CASREACT Full-text
Enantioselective total synthesis of epothilone A using
multifunctional asymmetric catalyses
Sawada, Daisuke; Shibasaki, Masakatsu TITLE:

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, 113-0033, Japan Angewandte Chemie, International Edition (2000), 39(1), 209-213 CODEN: ACIEFS; 1SSN: 1433-7851 AUTHOR(S): CORPORATE SOURCE: SOURCE:

Wiley-VCH Verlag GmbH Journal English PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

SN 10/563058 Page 149 of 172 STIC STN SEARCH RESULTS

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY * AVAILABLE VIA OFFLINE PRINT *

RX(8) RCT T 219990-25-7

STAGE(1) SOL 68-12-2 DMF STAGE(2) RGT D 144-55-8 NaHCO3, Z 26386-88-9 (PhO)2P(0)N3

PRO I 219989-84-1 REFERENCE COUNT: 3

THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ACCESSION NUMBER:
133:321737 CASREACT FULL-teat
ANOVELAPPLICATION of a PG(0)-Catalyzed Nucleophilic
Substitution Reaction to the Regio- and
Stereoselective Synthesis of Lactam Analogues of the
Epothilone Natural Products
Borzilleri, Robert M.; Zheng, Xiaoping; Schmidt,
Robert J.; Johnson, James A.; Kim, Scong-Hoon;
Dimarco, John D.; Fairchild, Craig R.; Gougoutas, Jack
Z.; Lee, Francis Y. F.; Long, Byron H.; Vite, Gregory
Divisions of Discovery Chemistry Oncology Drug

CE: Divisions of Discovery Chemistry Oncology Drug Discovery and Analytical Research and Development, Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, NJ, 08543-4000, USA Journal of the American Chemical Society (2000), 122(37), 8890-8897

SOURCE:

CODEN: JACSAT; ISSN: 0002 American Chemical Society Journal

PUBLI SHER:
DOCUMENT TYPE:
JOI
LANGUAGE:
En

SN 10/563058 Page 150 of 172 STIC STN SEARCH RESULTS

Several lactem analogs of the epothilones were prepared using a concise semisynthetic approach starting with the unprotected natural products. Highlighted in this strategy is a novel regio- and stereoselective PG(0)-catalyzed azidation reaction of a macrocyclic lactone. Subsequent reduction and macrolactemization of the resulting azide acid intermediates provided the desired macrolactems in satisfactory overall yields. The entire three-step sequence was streamlined into a "one-pot" process for the epothilone B-lactem, BMS-247550 (I), which is currently undergoing phase I clin. trials. An initial total synthesis route to propare the lactem analog of epothilone C was completed and compared to the more direct semisynthesis approach. All of the lactem analogs were evaluated in vitro and the results are discussed.

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RX(10) OF 115 ... AJ ===> AL...

(10)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(10) RCT AJ 219990-25-7

STAGE(1) RGT AM 26386-88-9 (PhO)2P(0)N3, AB 144-55-8 NaHCO3 SOL 68-12-2 DME

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<u>2</u>

AVAILABLE VIA OFFLINE PRINT * STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY -

CG 188730-19-0 RCT RX(27)

RGT CS 4136-95-2 2,4,6-C13C6H2COC1, BE 121-44-8 Et3N SOL 109-99-9 THF STAGE(1)

STAGE(2)

RGT BF 1122-58-3 4-DMAP SOL 108-88-3 PhMe

STEREOSELECTIVE CR 186692-84-2 PRO CR NTE STI REFERENCE COUNT:

THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

133:362657 CASREACT Full-text A process for the reduction of oxiranyl epothilones to Kim, Soong-Hoon; Johnson, James A. Bristol-Myers Squibb Co., USA COPYRIGHT 2007 ACS on STN olefinic epothilones CASREACT L90 · ANSWER 17 OF 28 ACCESSION NUMBER: TITLE:

PCT Int. Appl., 19 pp. CODEN: PIXXD2 INVENTOR(S):
PATENT ASSIGNEE(S):
SOURCE:

English Patent DOCUMENT TYPE: LANGUAGE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

APPLICATION NO. DATE KIND PATENT NO.

SG. U.S. ਲ੍ਹੇ કું ફુ WO 2000-US13253 86, GD, 88 % KZ, ¥,ï AZ, ES, 20001130 ₩, ĸĠ, A, AE, AL, CZ, DE, IN, IS, MD, MG, WO 2000071521

STIC STN SEARCH RESULTS SN 10/563058 Page 148 of 172

PT, 병송 83 NL, SE, MC, ZW BE, CH, C SE, BF, E 200002 0010912 9971204 GR, IT, LI, LU, JP 2000-619778 IN 2001-M1106 MX 2001-PA11053 US 1999-316796 US 1997-67549P US 1998-82563P US 1998-170581 CA 2000-2375029 EP 2000-930725 UA, UG, UZ, VN, Y SL, SZ, TZ, UG, Z IE, IT, LU, MC, N 8 MARPAT 133:362657 FR, 20011120 20001130 20020213 DK, ES, FI, RO 20030107 20070420 20020722 35, 38, TR, TJ, TM, KE, LS, I FI, FR, 님 . PRIORITY APPLN. INFO.: SL, GM, ES, JP 2003500394 IN 2001MN01106 MX 2001PA11053 AT, BE, sк, к, US 6320045 CA 2375029 EP 1178968 OTHER SOURCE(S): GI

via reduction of the corresponding 12,13-epoxyepothilones using a metal or metal-assisted reagent was selected fracta-essisted reagent was selected for group consisting of reactive metallocenes, [NZC(COZMe)2, cat RhZ(OAc)4] (NZC(COZMe)2, cat [(n-C7H15COZ)2Rh]2], [Zn-Cu, EtOH], [Mg(Hg), MgBr], Cr, dichloride in THF to give epothilone C, a 12(13)-(2)-olefin, in 80% yield reduced using magnesium turnings and [TIC13, LiAlH4], [TIC14, Zn], [WC16,], or [WC16, n-Buli]. Thus, epothil. cycloalkyl; R7 = H, alkyl, FeCl3, n-BuLil NeALH4], 2

RX(8) OF 18

8,4,8,i

SN 10/563058 Page 145 of 172 STIC STN SEARCH RESULTS

these lactams. Using our fully synthetically derived lactams, in vitro and in vivo studies were conducted in comparison with advanced clin. candidates, 12,13-desexyepothilone B and 12,13-desexyepothilone F, also derived by total efficient and was amenable to the production of significant quantities of

. k V 1000 þ RX(2) OF 2

<u>2</u>

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT * STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

RCT J 350042-12-5 RX (2)

M 7087-68-5 EtN(Pr-1)2, N 148893-10-1 1H-1,2,3-Triazolo[4,5hexafluorophosphate(1-), 3-oxide, 0 39968-33-7 3H-1,2,3-Triazolo(4,5-b)pyridine, 3-hydroxy-68-12-2 DWF, 75-09-2 GH2CL2 b]pyridinium, 1-[bis(dimethylamino)methylene]-, STAGE (1) SOL

STAGE (2)

RGT P 64-19-7 ACOH SOL 7732-18-5 Water, 109-99-9 THF

THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT PRO K 277749-43-6, L 350042-20-5 REFERENCE COUNT: 29 . THERE NO 20

CASREACT COPYRIGHT 2007 ACS on STN CASREACT

134:56502 L90 ANSWER 16 OF 28 ACCESSION NUMBER: TITLE:

CORPORATE SOURCE: AUTHOR(S):

Synthesis of Epothilones A and B Using Multifunctional Asymmetric Catalysis Sawada, Daisuke; Kanai, Motomu; Shibasaki, Masakatsu Graduate School of Pharmaceutical Sciences, The Enantioselective Total

145

SN 10/563058 Page 146 of 172 STIC STN SEARCH RESULTS

University of Tokyo, Bunkyo-ku Tokyo, 113-0033, Japan Journal of the American Chemical Society (2000), 122(43), 10521-10532 PUBLISHER: DOCUMENT TYPE:

SOURCE:

CODEN: JACSAT; ISSN: 0002-7863 American Chemical Society Journal English

LANGUAGE: GI

the conjugate addition of a thiol to an α,β -unsatd. thioester has been achieved. Epothilones A and B were divided into fragment A (I), fragment B (II), and fragment C (III). A catalytic asym. synthesis of fragments A and B aldol reaction of an unmodified ketone with an aldehyde, and a protonation in by Yamaguchi lactonization as key steps led to an enantiocontrolled synthesis of epothilone A. On the other hand, Suzuki cross_coupling of fragment B with ysis such as a cyanosilylation of an aldehyde, an the use of a direct catalytic asym. aldol reaction of an unmodified extens with an aldehyde as a key step, and the other utilizes a catalytic asym. protonation in the conjugate addition of a thick the sym. fragment A with fragment C followed was accomplished using a catalytic asym. cyanosilylation as a key step. synthesis of epothilones A and B using fragment C followed by Yamaguchi lactonization accomplished an enantiocontrolled synthesis of epothilone B Suzuki cross-coupling of An enantioselective total as a key step. 8

8 RX(27) OF 319

SN 10/563058 Page 143 of 172 STIC STN SEARCH RESULTS

TITLE:

Methodology based on chiral silanes in the synthesis of polypropionate-derived natural products - total synthesis of epothilone A Zhu, Bin; Panek, James S. R. W. Johnson Pharmaceutical Research Institute, Rafitan, NJ, 08669, USA AUTHOR(S): CORPORATE SOURCE:

European Journal of Organic Chemistry (2001), (9), 1701-1714

SOURCE:

CODEN: EJOCFK; ISSN: 1434-193X Wiley-VCH Verlag GmbH Journal English PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

Epothilones A and B are natural products with potent antitumor activity. These Bond construction methodol. based on chiral silanes was utilized to introduce the key C6 and C7 stereocenters of fragment I. A lipase-mediated kinetic the key C6 and C7 stereocenters of fragment I. A lipase-mediated kinetic resolution established the C15 stereocenter of fragment II. The 16-membored compds. have a Taxol-like mechanism of action against tumor cells. A total synthesis of epothilone A is reported, which is based on the synthesis and union of two advanced fragments: C3-C11 fragment I and C12-C21 fragment II. an aldol condensation, and a Yamaguchi-type lactone was constructed using a three-step sequence: an intermol. Suzuki coupling of I and II, macrolactonization reaction. 9

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AD.

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SN 10/563058 Page 144 of 172 STIC STN SEARCH RESULTS

9

AE YIELD 738

AD 297131-85-2 AF 121-44-8 Et3N, AG 4136-95-2 2,4,6-Cl3C6H2COCl AE 297131-86-3 RCT PRO SOL RX (6)

THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT 109-99-9 THF REFERENCE COUNT:

135:107175 CASREACT Full-text On the Interactivity of Complex Synthesis and Tumor COPYRIGHT 2007 ACS on STN CASREACT L90 ANSWER 15 OF 28 ACCESSION NUMBER: TITLE:

Pharmacology in the Drug Discovery Process: Total Synthesis and Comparative in Vivo Evaluations of the 15-Aza Epothilones Stachel, Shawn J.; Lee, Chul Bom; Spassova, Maria; Chappell, Mark D.; Bornmann, William G.; Danishefsky, Samuel J.; Chou, Ting-Chao; Guan, Yongbiao Laboratories for Bioorganic Chemistry Preclinical CORPORATE SOURCE: AUTHOR(S):

Facility, The Sloan-Kettering Institute for Cancer, Pharmacology and the Preparative Synthesis Core

Research, New York, NY, 10021, USA Journal of Organic Chemistry (2001), 66(12), 4369-4378 CODEN: JOCEAH; ISSN: 0022-3263 American Chemical Society English DOCUMENT TYPE: PUBLI SHER: LANGUAGE: SOURCE:

We have also successfully exidized 12,13,15-desexy-15(S)-eza-epothilone B to aza-epothilone B (aza-EpoB) EpoB-lactam). Aza-epothilone B has been advanced to phase I clin. trials by the Bristol-Myers Squibb group. Our synthesis is dEpoB-lactam) and 12,13,15-desoxy-15(R)-aza-epothilone B (15-epi-aza-dEpoB; 15-epi-dEpoB-lactam) have been accomplished via a highly convergent strategy. The total syntheses of 12,13,15-desoxy-15(S)-aza-epothilone B (aza-dEpoB;

SN 10/563058 Page 141 of 172 STIC STN SEARCH RESULTS

PRO K 219989-84-1.
NTE alternative pre

alternative prepn. gave lower yields
THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS
RECORD, ALL CITATIONS AVAILABLE IN THE RE FORWAT

COPYRIGHT 2007 ACS on STN CASREACT L90 ANSWER 13 OF 28 ACCESSION NUMBER: TITLE:

135:180640 CASREACT Full-text
The 12,13-diol cyclization approach for a truly
stereocontrolled total synthesis of apothilone B and
the synthesis of a conformationally restrained analog

Martin, Harry J.; Pojarliev, Peter; Kahlig, Hanspeter; Institut fur Organische Chemie der Universitat Wien,

CORPORATE SOURCE:

SOURCE:

AUTHOR(S):

Vienna, 1090, Austria Chemistry--A European Journal (2001), 7(10), 2261-2271 CODEN: CEUJED; ISSN: 0947-6539

Wiley-VCH Verlag GmbH

PUBLISHER: DOCUMENT TYPE: LANGUAGE:

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

2

diastereoselective aldol addition of epoxy-aldehyde IV and the known Southern methylene bridge to give a cyclohexanone derivative Thus, the Northern hemisphere aldehyde IV was added to the enolate of a cyclohexanone derivative carbon skeleton, containing all the stereogenic centers of I. Functional group manipulation, macrolactonization and removal of two protecting groups then vielded I. The spatial closeness of the C4- β -Me and C6-Me group in the been developed. The epoxide moiety in I was generated by regioselective mesylation and base treatment of the 12,13-diol II which was formed by a chelate Gram controlled Grignard addition of (3S)-Br(GH2)3GHMeCH:GH2 and Me Further manipulations and macrolactonization delivered the conformationally hemisphere ketone (S)-MeCH2COCMe2CH(OSiMe2CMe3)CH2CH:CH2 delivered the full A highly convergent and stereocontrolled synthesis of epothilone B (I) has Both fragments were synthesized from the chiral carbon pool to connect them through precursors (S)-citronellol and (S)-lactic acid, I inspired the authors then yielded I. The spatial closeness of crystal structure of I inspired the autho restrained epothilone derivative V.

RX(2) OF 2

SN 10/563058 Page 142 of 172 STIC STN SEARCH RESULTS

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

PAGE 1-B

H YIELD 658

121-44-8 Et3N, J 4136-95-2 2,4,6-Cl3C6H2COCl, K 1122-58-3 G 263761-19-9 4-DMAP RX(2)

263761-23-5 PRO

108-88-3 PhMe SOL

THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT REFERENCE COUNT:

L90 ANSWER 14 OF 28 CASREACT COPYRIGHT 2007 ACS ON STN ACCESSION NUMBER: 135:137326 CASREACT FULL-text:

SN 10/563058 Page 139 of 172. STIC STN SEARCH RESULTS

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA ÓFFLINE PRINT *

RX(8) RCT X 219990-25-7 RGT AC 26386-88-9 (PhO)2P(0)N3, J 144-55-8 NaHCO3 PRO AB 219989-84-1

SOL 68-12-2 DMF
REFERENCE COUNT: 89 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

ACESSION NUMBER: 12 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
135.257087 CASREACT Full-teak
TITLE: A process for the preparation of epothilone analogs
and intermediates
INVENTOR(S): Li, Wen Sen; Thornton, John E.; Guo, Zhenrong;
Swaminethan, Shankar; McConlogue, Gary W.
Bristol-Myers Squibb Company, USA
COUNCE: CONCE: CONCESSIONERS: PIXXD2
DOCUMENT TYPE: Patent

CODEN: PIXXD2
CODENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

多类异岛类 # Q GB, GR, IT, LI, LU, NL, SE, MC, PT, CY, AL, TR 7H, RS, 128, UZ, UZ, SE, TG R. P. S. 20010312 20010312 20010312 20020808 AT, UG, ZW, I MC, NL, I NE, SN, I CA 2001-2404212 EP 2001-918544 MX 2002-PA9165 US 2000-528526 WO 2001-US7749 APPLICATION NO. WO 2001-US7749 HU 2003-693 JP 2001-568920 NO, SL, SZ, TZ, U IE, IT, IU, N GW, ML, MR, N 7Z, MW, MX, IM, IR, 8, 8, 8, 20010927 20021218 , DK, ES, FR, , FI, RO, MK, 20030924 20050304 AU, JP, MK, SL, 9 8 X 2001002 20040812 LS, MW, FI, FR, CI, CM, AT, IS, MG, SK, R: AT, BE, CH, DE, IE, SI, LT, LV, ₹8 SI & IS KIND ES, CG, PRIORITY APPLM. INFO.: HU 200300693 JP 2003528090 IN 2002MN01074 MX 2002PA09165 ξ, £, WO 2001070716 **表现的分类级型** Ŕ CA 2404212 EP 1265878 PATENT NO. RW:

MARPAT 135:257087

OTHER SOURCE(S): GI

SN 10/563058 Page 140 of 172 STIC STN SEARCH RESULTS

AB The present invention relates to a process for the preparation of opothilone analogs, such as I (RRI = NH), by initially forming novol injectomed epothilones and carrying out a macrolactamization reaction thereon. The subject process is amenable to being carried out in a single reaction vessel without isolation of the intermediate compound and provides at least about a three-fold increase in yield over prior processes for preparing the desired epothilone analogs. Thus, ting opening of epothilone B was achieved using NaN3, PMe3 and Bu4N+Cl- in THF in the presence of Pd2(dba)3.CHCl3 to form TBA salt I (R = NH2, RI = O-.Bu4N+) in 93% yield. The ring opened epothilone B TBA salt the underwent intramol. macrolactamization using K2CO3, HOBE, and EDCI in THF and DMF to form lactam I (RRI = NH) in 92.7% % yield.

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

RX(2) RCT C 361204-09-3

STAGE(2) RGT M 2592-95-2 1-Benzotriazolol, N 25952-53-8 EDAP

SN 10/563058 Page 137 of 172 STIC STN SEARCH RESULTS

SOL 109-99-9 THF

STAGE(2) RGT AW 1122-58-3 4:

RGT AW 1122-58-3 4-DMAP SOL 108-88-3 PhMe

PRO AU 241129-40-8

L90 ANSWER II OF 28 CASREACT COPPRIGHT 2007 ACS on STN
ACCESSION NUMBER: 135:37156 CASREACT Full-teaxt
FITLE: Process for reduction of oxtranyl epothilones to olefinic epothilones
INVENTOR(5): Kim, 'Soong-hoon, James A.
FATENT ASSIGNEE(5): Bristol-Myers Squibb Co., USA
SOURCE: CODEN: USXXAM
DOCUMENT TYPE: CODEN: USXXAM
English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

CR, CU, ID, IL, LV, MA, SG, SI, CY, BE, GR, IT, LI, LU, NL, SE, MC, PT, SE, BF, 1 20000515 20000515 US 1999-316796 CA 2000-2375029 WO 2000-US13253 HU 2002-1467
JP 2000-619778
IN 2001-MN1106
MX 2001-PA111053
US 1997-67549P
US 1998-82563P
US 1999-316796
WO 2000-US13253 APPLICATION NO. EP 2000-930725 AT, BE, CH, DE, DK, ES, FR, GB, IE, SI, II, IV, FI, RO 20021028 20030107 20070420 20020722 ₽, 9 KIND PRIORITY APPLN. INFO.: HU 2002001467 JP 2003500394 IN 2001MN01106 MX 2001PA11053 US 6320045 CA 2375029 WO 2000071521 PATENT NO.

OTHER SOURCE(S): MARPAT 135:371566 GI

R7 R6 R4 OP2

SN 10/563058 Page 138 of 172 STIC STN SEARCH RESULTS

This process produced epothilones I (W = O, NRB; RL-R6 = H, (un)aubstituted alkyl, arkl, or aryl and R1 and R2 can be cycloalkyl; R7' = H, (un)substituted alkyl, aryl, cycloalkyl or 4-7 membered heterocyclic N-, O-, or S-containing rings; R8 = H, (un)unaubstituted calkyl, OH, (un)unsubstituted O-alkyl; X = CH=CH; Z = H or OPI where Pl, P2 = H, (un)substituted alkyl, alkanoyl, aroyl, trialkyl(aryl)silyl) from cxiranyl apothilones via the reaction of the oxiranyl moiety with a metal or metal-assisted reagent selected from the group consisting of reactive metallocenes, or (WCl6, n-Buil). Thus II was prepared in 29% yield in a multistep reaction from epothilone by the consisting of reactive metallocenes with the oxiranyl assapothilone intermediate which was reacted with WCl6 in THF and n-Buil in hexane.

RX(8) OF 16 ...X ===> AB...

SN 10/563058 Page 135 of 172 STIC STN SEARCH RESULTS

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																														PRI							OTH GI	

AB The present invention relates to compds., such as I, made by a subset of modules from one or more polyketide synthase ("PKS") genes that are used as starting material in the chemical synthesis of novel moli., particularly naturally occurring polyketides or derive, thereof. The biol. derived intermediates ("bio-intermediates") generally represent particularly difficult compds. to synthesize using traditional chemical approaches due to one or more

135

SN 10/563058 Page 136 of 172 STIC STN SEARCH RESULTS

stereocenters. In one aspect of the invention, an intermediate in the synthasis of epothilone is provided that feeds into the synthetic protocol of banishefsky and co-workers. In another aspect of the invention, intermediates in the synthesis of discodermolide are provided that feed into the synthesic of protocol of Smith and co-workers. By taking advantage of the inherent stereochem, specificity of biol, processes, the syntheses of key intermediates and thus the overtall syntheses of compds. Like epothilone and discodermolide are greatly simplified.

RX(12) OF 142 ... AQ ===> AU...

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RX(12) RCT AQ 241129-39-5

STAGE(1)
RGT AV 4136-95-2 2,4,6-C13C6H2COC1, E 121-44-8 Et3N

SN 10/563058 Page 133 of 172 STIC STN SEARCH RESULTS

PATENT NO.	KIND DATE	DATE	APPLICATION NO. DATE	DATE
	1			1 1 1 1 1 1 1 1
DE 10041470	A1	A1 20020228	DE 2000-10041470 20000818	20000818
PRIORITY APPLA. INFO.:	•:		DE 2000-10041470 20000818	20000818
OTHER SOURCE(S):	Æ	MARPAT 136:216592		
В				

$$x^1 = \frac{(CH2) \, n \cdot o}{(CH2) \, m - \frac{1}{1} \, (CH2) \, p R^2 6}$$

$$x^2 = (CH_2)_{in} - (CH_2)_{DR^2}6$$

2

According to invention, I can be used alone or for the achievement of additive or synergistic effects in combination with further principles and substance classes applicable in the tumor therapy. Exptl. data from patents ..tplbond.C-(CH2)pR26, (CH2)m-C:C-(CH2)pR26, X1, X2; n = 0 - 5; p = 0 - 3; m = 1 R2b = (CH2)m-C:tplbond.C-(CH2)pR26, (CH2)m-C:C- (CH2)pR26, X1, X2; R3a microtubulins (no data). I are able specifically to affect cell division and are suitable, for example for the treatment of malignant tumors ovarial -, stomach -, colon -, adeno -, chest -, lungs -, head and neck carcinoma, aryl, 0-502-aralkyl; R26 = H, CI-10-alkyl, aryl, Gr^2 20-aralkyl, CI-10-acyl, OH, 0-protecting group; R29 = H, CI-20-alkyl; R32 = H, CI-4-alkyl, CI-4-acyl; R33 = H, halogen), which interact with tubulins by stabilizing the formed = H, Ci-10-alkyl, aryl, C7-20-aralkyl; R3b = 0-protecting group; R4 = H, C1-10-alkyl, aryl; C7-20-aralkyl, halogen, OH, O-protecting group, CN; R5 = H, C1-10-alkyl, aryl, C7-20-aralkyl, (GH2)s-T; S = 1 - 4; T = OH, O-protecting malignant melanoma, acute lymphocytic and myelocytic leukemia. In addition I are suitable for the anti-angiogenesis therapy as well as for the treatment group, halogen; R6R7 = C(R33)2, NR32 A = OC(10), OCHZ, CH2C(10), NR29C(10), NR29SO2; DE = CH2CH2, CH2O, OCH2; G = K:CR8-, bicyclic or tricyclic aryl; X O, (0-alkyl)2, etc.; Z = H, H,OH, H,O-protective group; R8 = H, halogen, CX, CI-20-alkyl, aryl, C7-20-aralkyl; R14 = H, OH, halogen, O-SO2-alkyl, 0-SO2chronic ignitable illnesses (psoriesis, arthritis). For the avoidance of uncontrolled cell rampant growths on as well as the better compatibility of The present invention describes new 6-alkenyl- and 6-alkynylepothilone nedical implants I can be up and/or brought into polymers materials. PCT/EP00/01333 and PCT/IB00/00657 are reproduced here.

SN 10/563058 Page 134 of 172 STIC STN SEARCH RESULTS

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

PAGE 2-A

å.

C 402476-95-3 RX(1)

56-37-1 PhCH2NEt3 Cl 7732-18-5 Water, 64-17-5 EtOH PRO CAT

Process for the biomediated preparation of COPYRIGHT 2007 ACS on STN 136:183657 CASREACT L90 ANSWER 10 OF 28 ACCESSION NUMBER: TITLE:

intermediates for use in the synthesis of polyketides, such as epothilone D and discodermolide Santi, Daniel V.; Ashley, Gary; Myles, David C. Kosan Biosciences, Inc., USA

PCT Int. Appl., 129 pp. CODEN: PIXXD2 Patent INVENTOR(S):
PATENT ASSIGNEE(S):
SOURCE: DOCUMENT TYPE:

English FAMILY ACC. NUM. COUNT: PATENT INFORMATION: LANGUAGE:

SN 10/563058 Page 131 of 172 STIC STN SEARCH RESULTS

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

RCT C 361204-09-3 RX(2) STAGE(1) RGT K 584-08-7 K2CO3 SOL 109-99-9 THF, 68-12-2 DMF

RGT L 2592-95-2 1-Benzotriazolol, M 25952-53-8 EDAP STAGE(2)

PRO J 219989-84-1 NTE alternative prepns. gave lower yields

L90 ANSWER 8 OF 28 CASREACT ACCESSION NUMBER: 136:

NEACT COPYRIGHT 2007 ACS on STN 136:318824 CASREACT Full-text Synthetic and semisynthetic analogs of epothilones:

chemistry and biological activity

Almann, Karl-Heinz; Blommers, Marcel J. J.; Caravatti, Glorgio; Florsheimer, Andreas; Nicolaou, Kyriacos C.; O'Reilly, Terrence; Schmidt, Alfred;

AUTHOR(S):

TA Oncology Research, Novartis Pharma AG, Basel, Schinzer, Dieter; Wartmann, Markus CORPORATE SOURCE:

CH-4002, Switz.

ACS Symposium Series (2001), 796(Anticancer Agents),

SOURCE:

CODEN: ACSMCB; ISSN: 0097-6156

American Chemical Society Journal PUBLISHER: DOCUMENT TYPE: LANGUAGE: AB Epothilone

this paper we present the synthesis of these analogs and we discuss the impact of such modifications on tubulin polymerization activity as well as vivo, we have investigated a series of structural modifications involving the are naturally occurring microtubule depolymn. inhibitors, which exhibit potent in vitro antiproliferative activity. Epothilone B is a 30-fold more potent inhibitor of human cancer cell growth than paclitaxel in paclitaxel-sensitive cancer cell lines and in paclitaxel-resistant lines exceeds paclitaxel activity by 102 - 103-fold. In addition, epothilone B exhibits potent in vivo antitumor activity even in multidrug-resistant tumor requirements for epothilone-mediated cytotoxicity and antitumor activity and to discover analogs with similar potency but perhaps better tolerability in spoxide site (C12/C13) and the heterocyclic side-chain of epothilones. models. In order to gain a better understanding of the structural inglish Epothilones A and B a which exhibit potent

8 **8** ∶ RX(32) OF 320

cytotoxicity in vitro.

SN 10/563058 Page 132 of 172 STIC STN SEARCH RESULTS

CP 335160-11-7 RCT RX (32) STAGE (1)

CS 429-41-4 Bu4N.F 109-99-9 THF

CT 4136-95-2 2,4,6-C13C6H2COC1, AP-121-44-8 Et3N, STAGE (2) RGI

1122-58-3 4-DWAP SOL 109-99-9 THF, 108-88-3 PhMs

RGT R 76-05-1 F3CC02H SOL 75-09-2 CH2C12 STAGE (3)

CR 188260-10-8 PRO CH REFERENCE COUNT:

THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD, ALL CITATIONS AVAILABLE IN THE RE FORMAT 35

Procedures for the production of 12,13cyclopropylepothione derivatives, as well as for their use in pharmaceutical preparations Schering Ag, Germany Ger. Offen., 64 pp. L90 ANSWER 9 OF 28 CASREACT ACCESSION NUMBER: 136:2 TITLE:

Patent PATENT ASSIGNEE(S): SOURCE: DOCUMENT TYPE:

German LANGUAGE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

SN 10/563058 Page 129 of 172 STIC STN SEARCH RESULTS

+ STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT.

PAGE 2-A

YIELD 338

DH 472962-13-3 AN 4136-95-2 2,4,6-C13C6H2COC1, AO 121-44-8 Et3N, AP 1122-58-3 I 472962-14-4', 109-99-9 THF, 108-88-3 PhMe SOL 10 NTE St REFERENCE COUNT: RX (30)

stereoselective, Yamaguchi macrocyclization
31 - THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS
7, RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

A process for the preparation of epothilone analogs and intermediates.
Li, Wen-Sen; Thornton, John E.; Guo, Zhenrong;
Smannathan, Shankar REACT COPYRIGHT 2007 ACS on STN 137:140388 CASREACT Full-text CASREACT L90 ANSWER 7 OF 28 ACCESSION NUMBER: PATENT ASSIGNEE (S): INVENTOR(S): SOURCE: TITLE:

Bristol-Myers Squibb Company, USA PCT Int. Appl., 41 pp. CODEN: PIXXD2 Patent English DOCUMENT TYPE:

LANGUAGE:

APPLICATION NO. KIND FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PATENT NO.

ទុំមុំមុំមុំខ្ល 4, F, 5 BE, SE, TD, ZW, AT, NL, PT, NE, SN, 20010201 20010905 3 8 3 8 5 2 8 8 8 8 .20020122 DATE MZ, TR, MC, 11, SZ, TZ, UG, ZI, RR, IE, IT, UJ, MR, RS, GQ, GW, ML, MI, MS, SOO1-775361 US 2001-946721 US 2001-775361 US 2001-775361 US 2001-96721 US 2002-52825 WO 2002-US1853 WO 2002-US1853 MX, KP, BG, KG, TJ, MK, MN, SK, SL, S., 20020808 티디 AL, AM, CU, CZ, I J. B. B. CF, US 6518421
US 2003004338
AU 2002240014
PRIORITY APPLN. INFO.: HR, RG, RG, WO 2002060904 RW:

MARPAT 137:140388 OTHER SOURCE(S):

SN 10/563058 Page 130 of 172 STIC STN SEARCH RESULTS

three-fold increase in yield over prior processes for preparing the desired epothilone analogs. Thus, ring opening of epothilone B was achieved using NaNO, PMOS and BudNCI in THF in the presence of Pd2(dba)3.CHCI3 to form TeX salt I [R = NH2, RI = 0-BudH+ (III)] in 93% yield. III underwent intramol. macrolactamization using K2CO3, HOBt, and EDCI in THF and DMF to form II in is amenable to being carried out in a single reaction vessel present invention relates to a process for the preparation of epothilons solation of the intermediate compound and provides at least about ones and carrying out a macrolactamization reaction thereon. 2

RX(2) OF 4

(S)

20010201 20010905

SN 10/563058 Page 127 of 172 STIC STN SEARCH RESULTS

<u>2</u>

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

8

C 361204-09-3 K 584-08-7 K2CO3, L 2592-95-2 1-Benzotriazolol, M 25952-53-8 deg C SUBSTAGE(1) room temperature -> 109-99-9 THF, 68-12-2 DMF 1 219989-84-1 RGT PRO SOL SOL RX (2)

SUBSTAGE(4) 8 hours, 0 deg C SUBSTAGE(5) 2 hours, 10 deg C SUBSTAGE (3)

THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT optimization study NTE OF REFERENCE COUNT:

L90 ANSWER 6 OF 28 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 137:310727 CASREACT Full-text
Chemical synthesis and biological evaluation of novel
epothilone B and trans-12,13-cyclopropyl epothilone B AUTHOR(S):

Nicolaou, K. C.; Ritzen, Andreas; Namoto, Kenji; Buey, Ruben M.; Diaz, J. Fernando; Andreu, Jose M.; Markus; Altmann, Karl-Heinz; O'Brate, Wartmann,

Department of Chemistry and Skaggs Institute for Chemical Biology, Scripps Research Institute, La Jolla, CA, 92037, USA Tetrahedron (2002), 58(32), 6413-6432 CODEN: TETRAB; ISSN: 0040-4020 CORPORATE SOURCE:

Elsevier Science Ltd. DOCUMENT TYPE: LANGUAGE:

PUBLI SHER:

SOURCE:

SN 10/563058 Page 128 of 172 STIC STN SEARCH RESULTS

H

epothilone B analogs, e.g. II, was accomplished. While the synthesis of the epothilone B analog I proceeded through a Stille coupling of a vinyl iodide substrate containing the epothilone macrocycle with the appropriate side chain stannane, that of the cyclopropyl analogs involved a convergent strategy in which a Nozaki-Hiyama-Kishi coupling was used as a means of introducing the side chains prior to Yamaguchi macrolactonization and final elaboration to the nvolving in vitro tubulin polymerization, affinity for the microtubule Taxol spothilones and shed further light on the structure-activity relationships The synthesized analogs were subjected to biol. evaluation In addition to the total synthesis of the thiomethyl thiazole side chain The results identified the methylthic thiazole side chain as a potency enhancing moiety for the assays. binding site and cell cytotoxicity target mols.

...DH ==== H.C... RX(30) OF 782

(30)

SN 10/563058 Page 125 of 172 STIC STN SEARCH RESULTS

RX (3)

252877-37-5 Synthase, epothilone SOL

r, 67-68-5 DMSO hours, 30 deg C, pH 5 7732-18-5 Wate

enzymic, recombinant epothilone thioesterase biotransformation,

domain used, phosphate-buffered soln., product distribution depends on reaction conditions

29 THERE ARE 29 CITED REFERENCES, AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT REFERENCE COUNT:

8

Bristol-Myers Squibb Company, USA ... 17 pp., Cont.-in-part of U.S. .Ser. No. 528,526, CODEN: USXXAM epothilone analogs Li, Wen Sen; Thornton, John E.; Guo, Zhenrong; COPYRIGHT 2007 ACS on STN 138:153369 CASREACT FULL-text Process for the preparation of Swaminathan, Shankar CASREACT L90 ANSWER 5 OF 28 PATENT ASSIGNEE(S): ACCESSION NUMBER: INVENTOR (S); SOURCE:

English Patent DOCUMENT TYPE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

20010201 20010905 20020122 DATE APPLICATION NO. US 2001-775361 US 2001-946721 WO 2002-US1853 20030211 KIND DATE US 2003004338 WO 2002060904 WO 2002060904 PATENT NO.

3 8 3 8 5 3 8 8 8 AT, ZK. FI, KR, MA, TX, Y. 8,3,¥ BG, KG, KG, £1,48 KE, KE, SI, AZ, DM, IS, SI, SU, SD, GB, AT, IL, IL, SE, ZA, CI, S & 3.5.¥ 유 유 유 우 품, #29.75.99 #29.75.99 RW:

SN 10/563058 Page 126 of 172 STIC STN SEARCH RESULTS

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11 20020812 31 20061017

MARPAT 138:153369

OTHER SOURCE(S): GI

compound and provides at least about a three-fold increase in yield over prior processes for preparing the desired epothilone analogs. Thus, epothilone B I (X = 0) was treated with NaN3 and Bu4N+Cl- in THF followed by addition of The resulting solution was stirred under an argon atmospheric for 19 h. to form ring opened salt II in 96% yield. Salt II was then dissolved in THF and DMF, cooled to -5° , treated with XCO3 and stirred for 5 min before adding HOBt and EDCI then stirring for 2 h at -5° to form lactam I (X =NH) in 56% amenable to bein carried out in a single reaction vessel without isolation of the intermediate water PMe3 in THF and equilibrated to 25° then addition of Pd2(dba)3.CHCl3. he subject process is macrolactamization reaction thereon. yield from

. RX(2) OF 4

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BE, SE, TD,

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SN 10/563058 Page 123 of 172 STIC STN SEARCH RESULTS ...DB ====> EC... RX(38) OF 219

(B)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

PAGE 2-A

FIELD 338

RCT DB 611168-66-2 RX (38)

DJ 4136-95-2 2,4,6-Cl3C6H2COCl, BD 121-44-8 Et3N 109-99-9 THF STAGE (1) SOL SOL

1 hour, 0 deg C

CF 1122-58-3 4-DMAP 108-88-3 PhMe 3 hours, 75 deg C STAGE(2) SOL SOL SOL

Yamaguchi raaction, addnl. stereoleomeric reactant present F: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT E 611168-68-4 PRO E 6
NTE Yam
REFERENCE COUNT:

L90 ANSWER 4 OF 28 CASREACY ACCESSION NUMBER: 138:3 TITLE: Epoth

REACY COPYRIGHT 2007 ACS on STN
138:316732 CASREACT FUll-text
Epothilone C Macrolactonization and Hydrolysis Are
Ecallyzed by the Isolated Thiosterase Domain of
Epothilone Polyketide Synthase

SN 10/563058 Page 124 of 172 STIC STN SEARCH RESULTS

AUTHOR(S):

Boddy, Christopher N.; Schneider, Tanya L.; Hotta, Kinya; Walsh, Christopher T.; Khoela, Chaitan Departments of Chemical Engineering, Chemistry and Bochemistry, Stanford University, Stanford, CA, 94305-5025, USA

CORPORATE SOURCE:

Journal of the American Chemical Society (2003),

125(12), 3428-3429 CODEN: JACSAT; ISSN: 0002-7863

American Chemical Society Journal

English PUBLISHER: DOCUMENT TYPE:

Epochilone C is produced by the combined action of one nonribosomal peptide synthetase (NRPS) and nine polyketide synthase (PKS) modules in a multienzyme system. The final step in the biosynthesis is the thioesterase (TE)-catalyzed It has been unclear whether demonstrate that the excised apothilone TE domain can catalyze the efficient cyclization of the N-acetylcysteamine thioester of seco-apothilone C to generate apothilone C (kcat/KM = $0.41\pm0.03\,\mathrm{min}-1\,\mathrm{mV}-1)$). The TE domain also catalyses the hydrolysis of both the N-acetylcysteamine thioester of secocyclorelease of epothilone from the EpoF protein. It has been unclear whori isolated PKS TE domains could exhibit macrolactonization activity. Here we epothilone C (kcat = 0.087 ± 0.005 min-1, KM = 291 ± 53 µM) and that of the epothilone C (kcat = 0.67 \pm 0.01 min-1, $KM = 117 \pm 5 \mu M$) to form seconpothilone C. LANGUAGE: AB Epotl

...H ====> A... RX(3) OF 8

PAGE 1-B

<u>@</u>↑

SN 10/563058 Page 121 of 172 STIC STN SEARCH RESULTS

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room temperature -> -5 deg C
                                        60-29-7 Et20, 75-09-2 CH2C12
CON 1 hour, room temperature
                                                                                                              room temperature
                                                       CON room temperature
                                                                                               7732-18-5 Water
                                                                                                                                                        109-99-9 THF
                          STAGE (5)
                                                                                   STAGE (6)
                                                                                                                                           STAGE (7)
                                                                                                                                                                                                    STAGE (8)
                                                                                                                                                          8 8
8
                                                                                                              8
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CB 4136-95-2 2,4,6-C13C6H2COC1 SUBSTACE(1) -5 deg C SUBSTACE(2) -5 deg C -> 0 deg C SUBSTACE(2) -5 deg C -> 0 deg C CC 1122-58-3 4-DMAP RGT CA 121-44-8 Et3N CON -5 deg C 108-88-3 PhMe STAGE (10) STAGE (9) SOL SOL NO 8 g

HERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS ' RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT PRO BW 867376-54-3, BX 867376-57-6 sixth stage quench NTE SI REFERENCE COUNT:

4 hours, room temperature

CASREACT COPYRIGHT 2007 ACS on STN 143:211773 CASREACT Full-text Method for synthesis of Epothilon B lactam derivative Peop. Rep. China Faming Zhuanli Shenqing Gongkai Shuomingshu, No pp. CODEN: CNXXEV Yan, Jialin Chinese Patent qiven LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: L90 ANSWER 2 OF 28 ACCESSION NUMBER: PATENT ASSIGNEE(S): SOURCE: DOCUMENT TYPE: INVENTOR (S): TITLE:

PRIORITY APPIN. INFO:

AB Epochilon B lactum derivative was syntheaized from Epothilone B via regional and stereo selective nitridization of the Epsilon B macrolide catalyzed by palladium tri-Ph phosphine. Epothilone B was first ring opened via nitridization teochion to obtain nitronic catd, then processed with tri-Ph phosphine to produce inino phosphorane, later hydrolyzed with ammonium hydrowide to form amino acid, and finally the amino acid was cyclized with DPPA and solid sodium bicarbonate to obtain the target product Epothilone B CN 2003-10112901 20031225 CN 2003-10112901 20031225 20041215 4 Lactam derivative QN 1554659

121

SN 10/563058 Page 122 of 172 STIC STN SEARCH RESULTS

^=== 9··· RX(3) OF 6

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT !

К 144-55-8 NaHCO3, L 26386-88-9 (PhO)2P(O)N3 J 219989-84-1 G 219990-25-7 RGT PRO SOL SOL RX (3)

68-12-2 DMF 24 hours, 4 deg C

COPYRIGHT 2007 ACS on STN L90 ANSWER 3 OF 28 CASREACT ACCESSION NUMBER: 139:3

139:301287 CASREACT <u>Full-text</u>
Design, synthesis, and biological properties of highly potent epothilone B analogues AUTHOR(S): TITLE

Nicolaou, K. C.; Sasmal, Pradip K.; Rassias, Gerasimos; Reddy, Mali Venkat; Altmann, Karl-Heinz; Wartmann, Markus; O'Brate, Aurora; Giannakakou, Ľ Department of Chemistry, The Skaggs Institute for Chemical Biology The Scripps Research Institute, I Paraskevi CORPORATE SOURCE:

Angewandte Chemie, International Edition (2003), 42(30), 3515-3520 CODEN: ACIEFS; ISSN: 1433-7851 Jolla, CA, 92037, USA SOURCE:

Wiley-VCH Verlag GmbH & Co. KGaA

PUBLI SHER:

APPLICATION NO.

KIND DATE

PATENT NO.

Epothilones have potent cytotoxicity against tumor cells. We directed our attention toward the synthesis and evaluation of a small designed library of epothilone B analogs. From the library, we found that 12,13-cis-cyclopropane methylsulfanyl epothilone B is extremely potent. English DOCUMENT TYPE: LANGUAGE: AB Epothilone

SN 10/563058 Page 120 of 172 STIC STN SEARCH RESULTS

RX(28) OF 58 ...BQ + BR ===> BW BX

PAGE 1-B

(38)

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

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PAGE 2-A

NELD 178

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

PAGE 2-A

He Ne

BX YIELD 33%

RX(28)

STAGE(2) SOL 75-52-5 MeNO2 CON room temperature

STAGE(3)
RGT BZ 109-79-5 BuSH
CON room temperature

STAGE(4). RCT BQ 867376-53-2, BR 867376-58-7 SOL 60-29-7 Et20

SN 10/563058 Page 117 of 172 STIC STN SEARCH RESULTS

RGT Z 1122-58-3 4-DWAP SOL 108-88-3 PhMe STAGE (2)

AH 240816-03-9 PRO

9 key step REFERENCE COUNT:

THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 7 OF 7 CASREACT ACCESSION NUMBER: 127: TITLE:

127:108793 CASREACT Full-teat
127:108793 CASREACT Full-teat
Stereoselective syntheses and evaluation of compounds in the 8-desmethylepothilone A series: some surprising observations regarding their chemical and biological properties

Balog, Aaron; Betinato, Peter; Su, Dai-Shi; Meng,

AUTHOR(S):

Dongfang; Sorensen, Erik; Danishefsky, Samuel J.; Zheng, Yu-Huang; Chou, Ting-Chao; He, Lifeng; Horwitz, Susan B.

Lab. Bioorganic Chem., Sloan-Kettering Inst. Cancer CORPORATE SOURCE:

Res., New York, NY, 10021, USA Tetrahedron Letters (1997), 38(26),:4529-4532 CODEN: TELEAY, ISSN: 0040-4039

Elsevier Journal DOCUMENT TYPE: PUBLI SHER: SOURCE:

The title compds. have been synthesized in a convergent way by recourse to Weiler type dianion construction. LANGUAGE: AB The t

===> i, T. RX(3) OF 15

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

SN 10/563058 Page 118 of 172 STIC STN SEARCH RESULTS

N 1122-58-3 4-DMAP RCT I 192370-80-2 RGT M 538-75-0 DCC, N PRO L 192370-81-3 SOL 67-66-3 CHCl3 RX (3)

THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT REFERENCE COUNT:

L90 ANSWER 1 OF 28 CASREACT COPYRIGHT 2007 ACS on STN CASREACT 143:422202 ACCESSION NUMBER:

Avery, Mitchell A.; Chittiboyina, Amar Gopal; Chada, Novel protecting reagents, protecting groups and methods of forming and using the same

INVENTOR(S):

TITLE:

Raji Reddy; Kache, Rajashaker; Jung, Jae Chui He University of Mississippi, USA PCT Int. Appl., 82 pp. CODEN: PIXXDZ PATENT ASSIGNEE(S):

Patent

DOCUMENT TYPE:

SOURCE:

English FAMILY ACC. NUM. COUNT: PATENT INFORMATION: LANGUAGE

M2 NA, SL, ZA, ZW, DE, GW, US 2004-555896P 20040323 APPLICATION NO. MARPAT 143:422202 20051027 £3,6,8 KIND SE, PRIORITY APPLN. INFO. 88 WO 2005100329 OTHER SOURCE(S): S. S. E. PATENT NO. RW:

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

TIX-Y reagents are 2, 3, and 4-trialkylsilylxylyl, triarylsilylxylyl or a combination of alkyl-aryl silylxylyl reagents [TIX reagents, I (R, R'', R''' alkyl, aryl), II (R, R'', R''' = alkyl, aryl) and III (R, R'', R''' = alkyl, Thus, epothilone derivative IV new protecting group onto a reactive site of a multifunctional compound The hydroxyl groups, amine groups, or thiol groups; methods of removing the TIX protecting groups; and intermediate compds. formed during any one of these methods. The invention further provides methods useful in producing aryl)), which carry a TIX protecting group for protecting alcs. as ethers, urethanes, carbonates, acetals; amines as carbamates or uress; and thiols a ethers or esters. The invention also provides methods of forming the 2, 3, New protecting reagents TIX-Y (Y = OCMHOC13, Cl, Br, I, NCO, OCOC1, OCH2C1, OTS, OMS, ONS, OTf) are provided that allow for the selective placement of and 4-TIX reagents; introducing the TIX protecting groups to mols. bearing epothilones and analogs and derivs. thereof. Ħ

117

SN 10/563058 Page 115 of 172 . STIC STN SEARCH RESULTS

STAGE(1)
RGT X 4136-95-2 2,4,6-C13C6H2COC1, O 121-44-8 Et3N
SOL 109-99-9 THF

STAGE(2) RGT Y 1122-58-3 4-DWAP SOL 108-88-3 PhMe

PRO W 226940-49-4 NTE key step LIO9 ANSWER 6 OF 7 CASREACT EMIL-TEXE

ACCESSION NUMBER:

131:199535 CASREACT FALL-TEXE

TOTAL 199535 CASREACT FALL-TEXE

AUTHOR(S):

Nicolaou, K. C.; King, N. P.; Finlay, M. R. V.; He, Y.; Nicolaou, K. C.; King, N. P.; Finlay, M. R. V.; He, Y.; Sarabia, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Ninkovic, S.; Hepworth, D.

CORPORATE SOURCE:

Chandraca Biology, The Scripps Research Institute for Chandral Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA

SOURCE:

CODEN: RECEP; ISSN: 0968-0896

PUBLISHER:

DOCUMENT TYPE:

Brotish

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However How he has bus shown by the how he had he how he had he how he had he h

AB A Stille coupling strategy has been utilized to complete a total synthesis of epothilone E from vinyl lodide I (R1 = I; R2 = H) and thiazolestannane II.

The central core fragment I (R1 = I; R2 = H) and its trans-isomer III (R3 = I) were prepared from triene IV (TRS = Sihe2CMe3) using ring-closing metathesis (RCM), and were subsequently coupled to a variety of alternative stannanes to

115

SN 10/563058 Page 116 of 172 STIC STN SEARCH RESULTS

provide a library of epothilone analogs I (RI = 2-(5-acetoxypenty)) thiazol-4-yl, 2-(methylthio) thiazol-4-yl, 2-piperidinchiazol-4-yl, 2-methyythiazol-4-yl, 1 (2-piperidinchiazol-5-yl, 2-methyythiazol-4-yl, 2-ethoxymethyl) thiazol-5-yl, 2-ethoxythiazol-4-yl, 2-(acetoxymethyl) thiazol-4-yl, 2-(acetoxymethyl) thiazol-4-yl, 2-thiazol-4-yl, 2-thiazol-4-yl, 2-thiazol-4-yl, 2-thiazol-4-yl, 2-ethylthiazol-4-yl, 2-thiayl) thiazol-4-yl, 2-piperidinazol-4-yl, 2-piperidinazol-4-yl, 2-piperidinazol-4-yl, 2-piperidinazol-4-yl, 2-piperidinazol-4-yl, 2-piperidinazol-4-yl, 2-piperidinazol-4-yl, 2-piperidinazol-4-yl, 2-piperidinazol-2-yl, thiazol-5-yl, 2-thiayly hiazol-4-yl, 2-thylthiazol-4-yl, 2-ethylthiazol-4-yl, 2-piperidinazol-4-yl, 2-thiayl, Ph.3-pyridyl, CH:C(OEt)Me-(Z)]. The Stille coupling approach was then used to prepare epothilone B analogs from the key macrolactone intermediate I (RI = I, RZ = CH2OH) which was itself synthesized by a macrolactonization based strategy.

RX(19) OF 264 ... BT amp AH...

AH YIELD 848

RX(19) RCT BT 240816-02-8

STACE(1)

RGT CB 4136-95-2 2,4,6-C13C6H2CCC1, BW 121-44-8 Et3N
SOL 109-99-9 THF

SN 10/563058 Page 113 of 172 STIC STN SEARCH RESULTS

PAGE 1-B

+ STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

RCT AY 298702-20-2 RX (12) STAGE(1)
RGT N 121-44-8 Et3N, BB 50-43-1 Benzoic acid, 2,4,6-trichlorosol. 109-99-9-77HF

RGT BC 1122-58-3 4-DMAP SOL 108-88-3 PhMe STAGE(2)

THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT PRO BA 298702-21-3 NTE STEREOSELECTIVE REFERENCE COUNT:

treatment of proliferative diseases.
Nicolaou, Kyriacos Costa: Hepworth, David; Finlay, Maurice Raymond Verschoyle; King, Nigel Paul Novartis A.-G., Shitz.; Novartis-Erfindungen Verwaltungsgesellschaft m.b.H.; Scripps Research Preparation of 16-desmethylepothilones for the ACT COPYRIGHT 2007 ACS on STN 132:49832 CASREACT Full-tegt CASREACT L109 ANSWER 5 OF 7 ACCESSION NUMBER: TITLE:

INVENTOR (S):

PATENT ASSIGNEE (S):

Institute

PCT Int. Appl., 31 pp. CODEN: PIXXD2

SOURCE:

DOCUMENT TYPE:

English

LANGUAGE:
FAMILY ACC, NUM. COUNT:
PATENT INFORMATION:

19990621 DATE APPLICATION NO. WO 1999-EP4299 9967253 A3 20000420 W: AE, AL, AM, AT, AU, AZ, 19991229 KIND DATE **A**2 WO 9967253 WO 9967253 PATENT NO.

STIC STN SEARCH RESULTS SN 10/563058 Page 114 of 172

IS, 8,8 IN, MG, SL, DE, СН, СХ, ВF, ВЈ, GM, HR, HU, ID, IL, LS, LT, LU, LV, MD, SD, SE, SG, SI, SK, BE, SE, ¥,ÿ,ä,¥ 935 GB, KZ, PL, US, SD, IE, FI, NZ, UG, € € κε, ελ, ες, ελ, ες, 8 & S EE,

19990621 19980622 19970904 19980622 19961213 VM, YU, ZA, ZM SZ, UG, ZW, AT, B LU, MG, NL, PT, S NE, SN, TD, TG US 1998-102602 AU 1999-102602 US 1999-122155P US 1999-124653P US 1996-32864P US 1997-856533 US 1997-923869 WO 1999-EP4299 20020430

MARPAT 132:49832 OTHER SOURCE(S): GI * STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

synthesis of I, as well as for the synthesis of epothilone B (II) and their intermediates. Thus, 16-desmethyldesoxyepothilone analog III was prepared via Yamaguchi macrolactonization of hydroxy acid IV. The compds. I can be used and methods of The invention relates to compds. I $\{X = bond, 0; Q = OH,$ e.g. in the treatment of proliferative diseases æ

ann M. ٦. RX(4) OF 46

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+ STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

RCT J 252986-91-7 RX (4)

113

BB, BG, BR, BY, CA, CH, CN, CU, CZ,

B,

SN 10/563058 Page 111 of 172 STIC STN SEARCH RESULTS

NTE STEREOSELECTIVE REFERENCE COUNT: 22

THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L109 ANSWER 3 OF 7 CASREACT ACCESSION NUMBER: 134

AUTHOR(S):

SOURCE:

EACT COPYRIGHT 2007 ACS on STN
134:4795 CASREACT FULL-text
Total Syntheses of Epothilones B and D
Mulzer, Johann, Mantoulidis, Andreas; Oehler,
Blasbeth Institut fuer Organische Chemie, Universitaet Wien,

Vienna, A-1090, Austria Journal of Organic Chemistry (2000), 65(22), 7456-7467 CODEN: JOCEAH; ISSN: 0022-3263 American Chemical Society CORPORATE SOURCE:

and D are described, starting from optically pure (S)-malic acid and Me (R)-3-hydroxy-2-methylpropionate. The synthesis is highly convergent by coupling the three fragments Cl-C6 (fragment D), \mathcal{O} -C10 (fragment C), and Cll-C21 (fragment B). Key steps are two stereoselective Wittig type olefinations to the microtubule stabilizing antitumor drugs epothilone B aldol addition to synthesize fragment D, and a sulfone anion allyl lodide alkylation to connect fragments B and C. Finally fragment D was attached to generate the 12,13- and 16,17-double bonds, an enantioselective Mukaiyama English Total syntheses of DOCUMENT TYPE: PUBLI SHER: LANGUAGE: AB Tota

TO: RX(34) OF 711

the B + C fragment via aldol addition

D D

33

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

RCT DL 193146-26-8 RX (34)

DN 1122-58-3 4-DMAP, DO 25952-53-8 EDAP, DP 71561-71-2 STAGE (1) RGI

11

SN 10/563058 Page 112 of 172 STIC STN SEARCH RESULTS 4-Me2NC5H4N.HC1 SOL .67-66-3 CHC13

STAGE(2)

H 189453-35-8

PRO H REFERENCE COUNT:

RGT AK 12125-02-9 NH4Cl SOL 7732-18-5 Water

THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

COPYRIGHT 2007 ACS on STN CASREACT L109 ANSWER 4 OF 7 ACCESSION NUMBER:

133;266634 CASREACT Full-text
Total Synthesis and Antitumor Activity of
12,13-Desoxyeopthilone F: An Unexpected Solvolysis
problem at Cl5, Mediated by Remote Substitution at C21
Lee, Chul Bom; Chou, Ting-Cheo; Zhang, Xiu-Guo; Wang,
Zhi-Guang; Kuduk, Scott D.; Chappell, Mark D.;
Stachsl, Shawn J.; Danishefsky, Samuel J.
Laboratory for Bloorganic Chemistry, The

AUTHOR(S):

TITLE:

Sloan-Kettering Institute for Cancer Research, New CORPORATE SOURCE:

Journal of Organic Chemiatry (2000), 65(20), 6525-6533 CODEN: JOCEAH; ISSN: 0022-3263 American Chemical Society PUBLISHER: DOCUMENT TYPE:

SOURCE:

A пем epothilone analog, 12,13-desoxyapothilone F (dEpoF, 21-hydroxy-12,13-desoxyapothilone B, 21-hydroxyapothilone D), маз synthesized and evaluated for antitumor potential. A convergent strategy employed for the semi-practical synthesis of 12,13-desoxyepothilone B (dEpoB) has been utilized to yield an The results amount of dEpoF sufficient for relevant biol. studies. English LANGUAGE: AB A nev

hydroxyl group at C21, exhibits advantages over other epothilones in terms of vitro assay reveal that this new analog is highly active against various tu cell lines with a potency comparable to that of dEpoB. In particular, the growth of resistant tumor cells is inhibited by dEpoF at concns. where in vivo activity is also promising. The new analog, containing an addnl. functionalizable handle to preliminary assessment produce other useful compds. for pertinent biol. studies is basically ineffective. A and can serve as a readily paclitaxel (Taxol) water solubility,

...AY ====> BA. RX(12) OF 128

SN 10/563058 Page 109 of 172 STIC STN SEARCH RESULTS

STAGE(2) SOL 108-88-3 PhMe

STAGE(3) RGT AV 1122-58-3 4-DMAP SOL 108-88-3 PhMe

PRO W 279226-97-0 NTE stereoselective REFERENCE COUNT: 25

THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT

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L109 ANSWER 2 OF 7 CASREACT COPPRIGHT 2007 ACS on STN
ACCESSION NUMBER: 134:29228 CASREACT Full-text
TITLE: A novel highly stereoselective total synthesis of epoch of the (128,13R) acetonide
AUTHOR(S): Multer, J.; Karig, G.; Pojarliev, P. Institut fur Organische Chemie der Universitat Wien,

AUTHOR(S): CORPORATE SOURCE:

Tetrahedron Letters (2000), 41(40), 7635-7638 CODEN: TELEAY; ISSN: 0040-4039

SOURCE:

Journal English

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

Stereoselective syntheses of epothilone B and its novel derivative I are described. Key steps are the formation of intermediate II via Sharpless ADreaction and Davis-Evans-hydroxylation. æ

Š i. RX(30) OF 447

SN 10/563058 Page 110 of 172 STIC STN SEARCH RESULTS

VIELD 508

RCT CI 312492-96-9 RX(30)

STAGE (1)

RGT CN 429-41-4 Bu4N.F SOL 109-99-9 THF

RGT CO 4136-95-2 2,4,6-Cl3C6H2COCl, AF 121-44-8 Et3N SOL 108-88-3 PhMe STAGE (2)

RGT CP 1122-58-3 4-DMAP SOL 108-88-3 PhMe STAGE(3)

PRO CM 312492-98-1

SN 10/563058 Page 107 of 172 STIC STN SEARCH RESULTS

L90

28 SEA FILE—CASREACT ABB—ON PLU—ON ("126.251010"/AN OR "127:1087
93"/AN OR "127:293040"/AN OR "128:101936"/AN OR "127:1087
93"/AN OR "127:293040"/AN OR "128:101936"/AN OR "129:189151"/AN OR "131:31819"/AN OR "131:31819"/AN OR "131:31819"/AN OR "131:31819"/AN OR "131:31819"/AN OR "131:31819"/AN OR "131:266529"/AN OR "133:266634"/AN OR "133:266631"/AN OR "133:266634"/AN OR "133:266631"/AN OR "134:29228"/AN OR "134:4795"/AN OR "134:59530"/AN OR "134:59530"/AN OR "134:59530"/AN OR "134:5959"/AN OR "1999:176999"/AN OR "2000:524041"/AN OR "2000:624041"/AN OR "2

=> d ibib abs fhit L109 1-7; d ibib abs fhit L90 1-28

L106 AND L43 L108 NOT L90

FILE=CASREACT ABB=ON FILE=CASREACT ABB=ON

21

L108

134:178371 CASREACT Full-text
Synthesis and biological evaluation of highly potent analogues of epothilones B and D Altmann, K.-H.; Bold, G.; Caravatti, G.; Florsheimer, Novartis Pharma AG, TA Oncology Research, Basel, Bioorganic & Medicinal Chemistry Letters (2000), 10(24), 2765-2768 CODEN: BMCLE8; ISSN: 0960-894X COPYRIGHT 2007 ACS on STN A.; Guagnano, V.; Wartmann, M. Elsevier Science Ltd. CH-4002, LI09 ANSWER 1 OF 7 CASREACT ACCESSION NUMBER: 134: CORPORATE SOURCE: DOCUMENT TYPE: LANGUAGE: GI AUTHOR(S): PUBLI SHER: TITLE: SOURCE:

SN 10/563058 Page 108 of 172 STIC STN SEARCH-RESULTS

AB A series of new epothilone B and D analogs incorporating fused hetero-aromatic side chains have been prepared The synthetic strategy is based on olefin I as the common integraediate and allows variation of the side-chain structure in a highly convergent and stereoselective menner. These epothilone analogs, e.g. II, are more potent inhibitors of cancer cell proliferation than the corresponding parent epothilones B or D.

RX(11) OF 370 ... AR ===> FF...

<u>:</u>

W YIELD 70% RX(11) RCT AR 279226-96-9

STAGE(1)
RGT .AT 4136-95-2 2,4,6-C13C6H2COCL, AU 121-44-8 Et3N
SOL 109-99-9 THF

105

SN 10/563058 Page 105 of 172 STIC STN SEARCH RESULTS

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6-18 8-19 10-20 11-21 11-22
                                                                                    7-8 8-9 8-19 9-10 10-11
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                                                                    3-4 4-5
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                   ring/chain nodes
                                                                              sxact/norm bonds
chain nodes
                                                                                                exact bonds
                                                                                                           2-13
                                                                                        2-3
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Match level:
1:CIASS 3:CIASS 4:CIASS 5:CIASS 6:CIASS 9:CIASS 9:CIASS
11:CIASS 2:CIASS 12:CIASS 13:CIASS 14:CIASS 15:CIASS 16:CIASS 17:CIASS 18:CIASS 19:CIASS 20:CIASS 20:CIAS

=> => d stat que 1109 ...

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation: Uploading 11.str

6-18 8-19 10-20 11-21 11-22 10-11 7-8 8-9 8-19 9-10 10-20 11-21 11-22 8-9 9-10 10-11 22 21 4-17 4-17 6-18 20 7-8 13 4-16 **6-**7 6-7 4-16 18 3-14 3-15 4-5 ring/chain.bonds exact/norm bonds chain nodes exact bonds chain bonds 2-12 2-13 ring/chain

Match level:
1:CLASS 2:CLASS 4:CLASS 5:CLASS 6:CLASS 9:CLASS 9:CLASS 1:CLASS 1:CLASS 17:CLASS 17:CLASS 17:CLASS 17:CLASS 17:CLASS 17:CLASS 20:CLASS 20:CLASS 21:CLASS 21:CLASS 22:CLASS 22:CLASS 22:CLASS 23:CLASS 23:CLASS 23:CLASS 23:CLASS 23:CLASS 24:CLASS 24:CLASS 24:CLASS 25:CLASS 25:CLASS

| 13 | 560 SEA FILE=REGISTRY SSS FUL | 1 | 22933 SEA FILE=REGISTRY ABB=ON PLU=ON CCL5/ES\$; | 12730 SEA FILE=REGISTRY ABB=ON PLU=ON CCL6/ESS | 123 | 726 SEA FILE=REGISTRY ABB=ON PLU=ON CL5/ESS | 124 | 50 SEA FILE=REGISTRY ABB=ON PLU=ON CL5/ESS | 12165 SEA FILE=CASREACT ABB=ON PLU=ON CL5/ESS | 12165 SEA FILES SEA

SN 10/563058 Page 103 of 172 STIC STN SEARCH RESULTS

STAGE(1)

RGT AW 1191-15-7 AlH(Bu-i)2

SOL 108-88-3 PhMe

STAGE(2)

RGT BK 7647-01-0 HCl

SOL 7732-18-5 Water, 67-56-1 MeOH

PRO BJ 226940-68-7

RX(16) RCT BL 187527-25-9

STAGE(1)

RGT BE 108-18-9 i-PrZNH, BF 109-72-8 BuLi
SOL 109-99-9 THF, 110-54-3 Hexane

STAGE(2)

RGT BJ 226940-68-7

SOL 109-99-9 THF

PRO BM 240815-96-7, BN 240815-97-8
REFERENCE COUNT:
60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS
RECORD, ALL CITATIONS AVAILABLE IN THE RE FORWAT

STAGE(3) RGT BO 64-19-7 ACOH SOL 109-99-9 THF

SN 10/563058 Page 104 of 172 STIC STN SEARCH RESULTS

=> file casreact

FILE 'CARREAT' ENTERED AT 12:18:14 ON 11 OCT 2007

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FILE CONTENT:1840 - 6 Oct 2007 VOL 147 ISS 16

New CAS Information Use Policies, enter HELP USAGETERMS for details.

CASREACT now has more than 13.8 million reactions

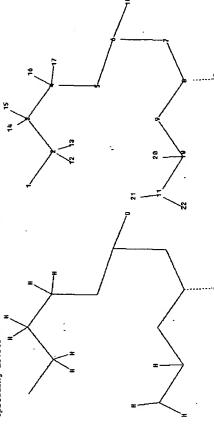
Some CASREACT records are derived from the ZIC/VINITI database (1974-1999) provided by InfoChem, INPI data prior to 1986, and Biotransformations database compiled under the direction of Professor Dr. Klaus Kieslich.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d stat que L90

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation: Uploading L1.str



RX(11)

2 BL

RCT BC 70113-32-5

RX(13)

BM YIELD 398

RX(14)

BN YIELD 278

SN 10/563058 Page 99 of 172 STIC STN SEARCH RESULTS

CAT 3144-16-9 10-CSA SOL 67-56-1 MeOH, 75-09-2 CH2Cl2

STAGE (2)

RGT H 87413-09-0 Martin's reagent SOL 75-09-2 CH2C12

AN 193146-27-9 (82%;97%) PRO

RCT V 185148-95-2

RX (22)

X 109-72-8 BuLi, Y 108-18-9 i-PrZNH RGT X 109-72-8 BuL1, Y 108-18-9 is SOL 109-99-9 THF, 110-54-3 Hexane STAGE (1)

STAGE (2)

RCT AN 193146-27-9 SOL 109-99-9 THF

PRO BY 210690-87-2, BZ 250284-01-6

NTE stereoselective key step

REFERENCE COUNT: 82 THERE ARE BZ CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT

æ

CASREACT L33 ANSWER 23 OF 23 ACCESSION NUMBER:

NREACT COPYRIGHT 2007 ACS on STN 173:199535 CASREACT Full-teat Total synthesis of epothlione E and related side-chain myddfield analoques via a Stille coupling based

strategy

Nicolaou, K. C.; King, N. P.; Finlay, M. R. V.; He, Y.; Roschangar, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Ninkovic, S.; Hépworth, D. Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA

CORPORATE SOURCE:

SOURCE:

AUTHOR(S):

Bioorganic & Medicinal Chemistry (1999), 7(5), 665-697

CODEN: BMECEP; ISSN: 0968-0896

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

SN 10/563058 Page 100 of 172 STIC STN SEARCH RESULTS

A Stille coupling strategy has been utilized to complete a total synthesis of epothilone E from vinyl iodide I (R1 = I; R2 = H) and thiazolestannano II.
The central core fragment I (R1 = I; R2 = H) and its trans-isomer III (R3 = I) were prepared from triene IV (TBS = SiMe2CM3) using ring-closing metathesis (RCM), and were subsequently coupled to a variety of alternative stannanos to provide a library of epothilone analogs I (R1 = 2-(5-acetoxypentyl)thiazol-4-2-ethylthiazol-4-yl, 2-furyl, 2-thienyl, Ph,3-pyridyl, CH:C(OEt)Me-(Z), RZ = H] and III (R3 = 2-(5-acetoxypentyl)thiazol-4-yl, 2-(methylthlo)thiazol-4-yl, 2-piperidinothiazol-4rilazol-5-yl, 2-(hydroxymethyl)thiazol-4-yl, 2-(acetoxymethyl)thiazol-4-yl, 2-(fluoromethyl)thiazol-4-yl, 2-furyl, (fluoromethyl)thiazol-4-yl, 2-vinylthiazol-4-yl, 2-ethylthiazol-4-yl y1, 2-(methylthio)thiazol-4-y1, 2-piperidinothiazol-4-y1, 2-methoxythiazol-4-y1, 2-ethoxythiazol-4-y1, thiazol-4-y1, thiazol-2-y1, thiazol-2-y1, thiazol-5-y1, thiazol-5-y1, 2-2-thienyl, Ph,3-pyridyl, $GH:C(OEt)Me-\{Z\}$. The Stille coupling approach was then used to prepare epothilone B analogs from the key macrolactone intermediate I (R1 = I, R2 = CH2OH) which was itself synthesized by a /l, 2-methoxythiazol-4-yl, 2-ethoxythiazol-4-yl, thiazol-4-yl, thiazol-2-yl, (hydroxymethyl)thiazol-4-yl, 2-(acetoxymethyl)thiazol-4-yl, 2-2-vinylthiazol-4-yl, macrolactonization based strategy thiazol-5-yl, 2 fluoromethyl

RX(132) OF 264 COMPOSED OF RX(10), RX(11), RX(12), RX(13), RX(14), RX(15), RX(132)
RX(132)
AM + 2 AR + 2 AU + 2 BC + 2 BL ===> BM + BM

BY YIELD 82%

SN 10/563058 Page 98 of 172 STIC STN SEARCH RESULTS

BZ YIELD 98

RCT AM 210690-85-0

RX(10)

SN 10/563058 Page 95 of 172 STIC STN SEARCH RESULTS

STAGE(5) SOL 109-66-0 Pentane

B 298702-07-5 STEREOSELECTIVE

RCT A 224580-52-3 RX(1)

RGT D 280-64-8 9-BBN SOL 109-99-9 THF STAGE (1)

STAGE (2)

B 298702-07-5 E 534-17-8 C52CO3, F 603-32-7 Ph3As 72287-26-4 Palladium, [1,1"-bis(diphenylphosphino-RGT CAT

KP) ferrocene]dichloro-, (SP-4-2)-

SOL 68-12-2 DMF

STAGE(3) SOL 7732-18-5 Water

C 298702-16-6 STEREOSELECTIVE PRO

RCT C 298702-16-6 RX (9)

AR 7647-01-0 HC1 67-56-1 MeOH STAGE (1)

STAGE(2)

RGT 0 144-55-8 NaHCO3 SOL 7732-18-5 Water

SOL 75-09-2 CH2C12 STAGE (3)

PRO AQ 298702-17-7 NTE STEREOSELECTIVE

AQ 298702-17-7, AS 67-56-1 RCT RX(10)

STAGE(1)

RGT AV 1333-74-0 H2 CAT 109361-17-3 Ruthenium, bis[(1R)-:[1,1'-binaphthalene]-2,2'diylbis (diphenylphosphine-kP)|di-µ-chlorodichloro(N,N-diethylethanamine)di-67-56-1 MeOH

SOL

RGT 0 144-55-8 NaHCO3 STAGE (2)

STAGE(3) SOL 75-09-2 CH2C12

THERE ARE 51 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT PRO AT 298702-18-8, AU 298702-19-9 COUNT: 51 THERE ARE 51 CI REFERENCE COUNT:

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SN 10/563058 Page 96 of 172 STIC STN SEARCH RESULTS

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131:351125 CASREACT Full-text
Syntheses of (-)-epothilone B
Schinzer, Dieter; Bauer, Armin, Schleber, Jonnifer,
Chemistere, Dieter; Bauer, Armin, Schleber, Jonnifer,
Chemistery—A European Journal (1999), 5(9), 2492-2500

Wiley-VCH Verlag GmbH CASREACT L33 ANSWER 22 OF 23 ACCESSION NUMBER: CORPORATE SOURCE: AUTHOR(S):

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI SOURCE:

synthesis on a macrolactonization. The key fragments are available on large scale to provide sufficient material for biol. tests. Thiszole fragment II (TBDMS = SiMe2CNe3) was obtained by an improved route starting from (8)-malic acid. The first synthesis is based on our preceding paper. The critical triaubstituted double bond (12-13 in our second approach was constructed by a highly efficient Pd-mediated coupling reaction. Ring closure was achieved by reported. One strategy is based on ring-closing metathesis, and a second synthesis on a macrolactonization. The key fragments are available on la Two efficient routes for the total synthesis of (-)-epothilone B (I) are macrolactonization. æ

RX(79) OF 215 COMPOSED OF RX(12), RX(21), RX(10), RX(22) RX(79) 2 AT + 2 AU + 2 AP + 2 V ===> BY + BZ

water solubility, and can serve as a readily functionalizable handle to produce other useful compds. for pertinent biol. studies.

RX(33) OF 128 COMPOSED OF RX(7), RX(1), RX(9), RX(10)
RX(33) 2 AG + 2 AH + 2 A + AS ====> AT + AU

AH

PAGE 1-B

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EP 107905-52-2
ES 17455-13-9 18-Crown-6, BJ 40949-94-8 K [N(SIMe3)2]
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            ED 218613-98-0
ES 17455-13-9 18-Crown-6, BJ 40949-94-8 K [N(SiMe3)2]
109-99-9 THF
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          CV 308357-81-5
CX 7588-79-4 Na2HPO4, CY 11110-52-4 Sodium amalgam
CX 7588-79-4 Na2HPO4, CY 11110-52-4 Sodium amalgam
CX 758-1 MeOH, 109-99-9 THF
SN 10/563058 Page 91 of 172 STIC STIN SEARCH RESULTS
                                                                                                                                                                                                                                                                      SOL 109-99-9 THF, 142-82-5 Heptane
                                                                                                                       RGT AK 12125-02-9 NH4C1
SOL 7732-18-5 Water, 60-29-7 Et20
                                                                                                                                                                                                                                                                                                                                    RGT AO 304-59-6 Rochelle salt
SOL 67-56-1 MeOH, 60-29-7 Et20
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   75-05-8 MeCN, 60-29-7 Et20
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SOL 7732-18-5 Water
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SOL 75-05-8 MeCN, 60-
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diastereomeric mixt.
                                           RGT ES 17455-13-9
SOL 109-99-9 THF
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                                                                                                                                                                                          stereoselective
                                                                                                                                                                         EU 218614-04-1
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SN 10/563058 Page 92 of 172 STIC STN SEARCH RESULTS

SOL 67-56-1 M6OH, 75-09-2 CH2C12

D 144-55-8 NAHCO3

STAGE(2) RGT D 144-55-8 NaHCX SOL 7732-18-5 Water

FA 193146-27-9 75-09-2 CH2C12, 110-86-1 Pyridine

d 187527-25-9

RCT

RX (57)

STAGE (1)

CZ 210690-99-6 BT 77-76-9 Me2C(OMe)2

RGT PRO SOL

RX (56)

CZ 210690-99-6

PRO.

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antitumor potential. A convergent strategy employed for the semi-practical synthesis of 12,13-desoxyspochilone B (dEpcB) has been utilized to yiold an amount of dEpcF sufficient for relevant biol. studies. The results from an invitro assay reveal that this new analog is highly active against various tumor cell lines with a potency comparable to that of dEpcB. In particular, the growth of resistent tumor cells is inhibited by dEpcB at concus. where paclitaxel (Taxol) is basically ineffective. A preliminary assessment of its in vivo activity is also promising. The new analog, containing an addnl.
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       A new epothilone analog, 12,13-desoxyapothilone F (dEpoF, 21-hydroxy-12,13-desoxyapothilone B, 21-hydroxyepothilone D), was synthesized and evaluated for
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         hydroxyl group at C21, exhibits advantages over other epothilones in terms of
                                                                                                                                                                                                                                                                                                                                                                                 PRO FB 193146-50-8, DB 193146-49-5
COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             Problem at C15, Mediated by Remote Substitution at C21 Lee, Chul Bom; Chou, Ting-Chao; Zhang, Xiu-Guo; Wang, Zhi-Guang; Kuduk, Scott D.; Chappell, Mark D.; Stachel, Shwn J.; Danishefsky, Samuel J. Laboratory for Bioorganic Chamistry, The Sloan-Kettering Institute for Cancer Research, New
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    Journal of Organic Chemiatry (2000), 65(20), 6525-6533 CODEN: JOCEAH; ISSN: 0022-3263
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     133:266634 CASREACT Full-teat
Total Synthesis and Antitumor Activity of
12,13-Desoxyepothilone F: An Unexpected Solvolysis
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               CASREACT COPYRIGHT 2007 ACS on STN
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RGT W 4111-54-0 Lin(Pr-1)2
SOL 109-99-9 THF
                                                                                                                                                                                                                                                  STAGE(3)
RGT AK 12125-02-9 NH4C1
SOL 7732-18-5 Water
                                                                                                                                      RCT FA 193146-27-9
SOL 109-99-9 THF
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            English
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               L33 ANSWER 21 OF 23
ACCESSION NUMBER:
                                                                                                            STAGE (2)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      CORPORATE SOURCE:
                                                                                                                                                                                                                                                                                                                                                                                                                                         REFERENCE COUNT:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       DOCUMENT TYPE:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  PUBLISHER:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              AUTHOR(S):
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 LANGUAGE:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  SOURCE:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              g
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PAGE 1-B

RCT ET 188899-14-1 RX (52)

SN 10/563058 Page 89 of 172 STIC STN SEARCH RESULTS

2 CU

PAGE 1-A

SN 10/563058 Page 87 of 172 STIC STN SEARCH RESULTS

PAGE 1-B

CJ YIELD 50% OPh.

RCT BG 188730-08-7, BH 4736-60-1 RX(15)

RGT BJ 109-72-8 BuLi SOL 109-99-9 THF STAGE(1)

STAGE(2) .RGT AZ 7553-56-2 I2

STAGE(3) RGT BK 1070-89-9 (Me3S1)2N.Na

PRO

BI 210690-66-7 STEREOSELECTIVE

BI 210690-66-7 BA 7664-39-3 HF, BB 110-86-1 Pyridine BL 312730-71-5 RX (16)

RCT RGT PRO SOL NTE

STEREOSELECTIVE

8

SN 10/563058 Page 88 of 172 STIC STN SEARCH RESULTS

BL 312730-71-5, BC 108-24-7 BE 121-44-8 Et3N, BF 1122-58-3 4-DMAP RCT RGT PRO SOL NTE RX(17)

BM 189453-18-7

STEREOSELECTIVE 75-09-2 CH2C12

RCT BV 262375-53-1, BM 189453-18-7 RX (26)

STAGE(1)

CM 280-64-8 9-BBN 109-99-9 THF RGT STAGE (2)

CM 7778-53-2 K3P04 72287-26-4 Palladium, (1,1'-bis(diphenylphosphinoκP) ferrocene]dichloro-, (SP-4-2)-68-12-2 DMF, 7732-18-5 Water CAT

SOL

PRO

CJ 312730-85-1 ULTRASOUND IN FIRST STAGE, STEREOSELECTIVE 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS 4T: RECORD, ALL CITATIONS AVAILABLE IN THE RE FORWAT REFERENCE COUNT: ME

SREACT COPYRIGHT 2007 ACS on STN 134:4795 CASREACT FULL-text Total Syntheses of Epothliones B and D . Mulzer, Johann; Mantoulidis, Andreas; Oehler, Elisabeth CASREACT L33 ANSWER 20 OF 23 ACCESSION NUMBER:

AUTHOR(S):

Institut fuer Organische Chemie, Universitaet Wien, CORPORATE SOURCE:

Vienna, A-1090, Austria Journal of Organic Chemistry (2000), 65(22), 7456-7467 CODEN: JOCEAH; ISSN: 0022-3263 American Chemical Society SOURCE:

Journal DOCUMENT TYPE: PUBLI SHER:

English LANGUAGE: AB Total

and D are described, starting from optically pure (S)-malic acid and Mo (R)-3-hydroxy-2-methylpropionate. The synthesia is highly convergent by coupling the three fragments Cl-C6 (fragment D), CJ-ClO (fragment C), and Cll-C21 (fragment B). Key steps are two stereqselective Wittig type olefinations to generate the 12,13- and 16,17-double bonds, an enantioselective Mukaiyama aldol addition to synthesize fragment D, and a sulfone anion allyl iodide alkylation to connect fragments B and C. Finally fragment D was attached to the microtubule stabilizing antitumor drugs epothilone B the B + C fragment via aldol addition Total syntheses of

RX(411) OF 711 COMPOSED OF RX(52), RX(61), RX(55), RX(28), RX(29), RX(56),

+ **\===** + 5 + 2 ED + 2 EP 2 12 RX (411)

SN 10/563058 Page 85 of 172 STIC STN SEARCH RESULTS

STAGE(1) RGT AW 4111-54-0 LiN(Pr-i)2 SOL 109-99-9 THF RCT AV 321522-36-5, AX 17341-93-4 RGT J 12125-02-9 NH4Cl SOL 7732-18-5 Water RCT AS 312492-69-6 SOL 109-99-9 THF PRO AV 321522-36-5 STAGE(2) STAGE(3) STAGE (1) RX(13)

RGT T 110-86-1 Pyridine SOL 75-09-2 CH2Cl2 STAGE(2) RGT Y 144-55-8 NaHCO3 SOL 7732-18-5 Water

PRO AY 321522-37-6 RCT AY 321522-37-6 RX(14)

RGT BA 20816-12-0 0s04, BB 7529-22-8 Me-morpholineoxide SOL 109-99-9 THF, 75-65-0 t-BuOH, 7732-18-5 Water STAGE(1) STAGE (2)

RGT V 7772-98-7 Na2S203 SOL 7732-18-5 Water, 75-09-2 CH2C12

RGT C 10028-15-6 Ozone SOL 64-17-5 EtOH, 7732-18-5 Water STAGE (3)

STAGE(4) RGT Y 144-55-8 NaHCO3 SOL 7732-18-5 Water

PRO AZ 321522-38-7

134:56502 CASREACT Full-text Enantioselective Total Synthesis of Epothilones A and COPYRIGHT 2007 ACS on STN L33 ANSWER 19 OF 23 CASREACT ACCESSION NUMBER: 134:56 TITLE: Enanti

B Using Multifunctional Asymmetric Catalysis Sawada, Dalsuke; Kanai, Mctomu, Shibasaki, Masakatsu Graduate School of Pharmaceutical Sciences, The University of Tokyo, Bunkyo-ku Tokyo, 113-0033, Japan Journal of the American Chemical Society (2000),

AUTHOR(S): CORPORATE SOURCE:

SOURCE:

122(43), 10521-10532 CODEN: JAÇSAT; ISSN: 0002-7863

American Chemical Society

Journal PUBLISHER: DOCUMENT TYPE: 8

English LANGUAGE:

SN 10/563058 Page 86 of 172 STIC STN SEARCH RESULTS

t-BuMe2Si

the conjugate addition of a thiol to an α,β -unsatd. thioester has been achieved. Epothilones A and B were divided into fragment A (1), fragment B (II), and fragment C (III). A catalytic asym. synthesis of fragments A and B was accomplished using a catalytic asym. cyanosliylation as a key step. An enanticcontrolled synthesis of fragment C was achieved in two ways. One is the use of a direct catalytic asym. aldol reaction of an unmodified ketone with an aldehyde as a key step, and the other utilizes a catalytic asym. of epothilone A. On the other hand, Suzuki cross-coupling of fragment B with fragment C followed by Yamaguchi lactonization accomplished an enanticontrolled synthesis of epothilone B. multifunctional asym. catalysis such as'a cyanosilylation of an aldehyde, an aldol reaction of an unmodified ketone with an aldehyde, and a protonation in protonation in the conjugate addition of a thiol to an α,β -unsatd. thioester as a key step. Suzuki cross-coupling of fragment A with fragment C followed by Yamaguchi lactonization as key steps led to an enantlocontrolled synthesis An enantioselective total synthesis of epothilones A and B using æ

RX(90) OF 319 COMPOSED OF RX(15), RX(16), RX(17), RX(26) RX(90) BG + BH + BC + BV ===> CJ

AZ YIELD 78%

AF 321522-34-3, G 67-56-1 AH 584-08-7 K2CO3 AI 263761-11-1 RGT PRG RX (8)

SN 10/563058 Page 84 of 172 STIC STN SEARCH RESULTS

SOL 67-56-1 MeOH NTE stereoselective

RCT AI 263761-11-1

RX(19)

STAGE(1) RGT AT 1191-15-7 AlH(Bu-1)2 SOL 75-09-2 CH2C12

STAGE(2) RGT J 12125-02-9 NH4C1 SOL 7732-18-5 Water

PRO AK 263761-13-3

RCT AJ 263768-73-6 RX (9)

STACE(1) RGT AM 109-72-8 BuLi SOL 60-29-7 Et20, 109-99-9 THF, 7732-18-5 Water

STAGE(2) RCT AK 263761-13-3 SOL 109-99-9 THF

STAGE(3) RGT J 12125~02-9 NH4Cl SOL 7732-18-5 Water

PRO AL 263761-14-4 RCT AL 263761-14-4 RX(10)

STAGE(1)
RGT AQ 38721-52-7 L-Selectride SOL 109-99-9 THF

STAGE(2) RCT AN 74-88-4 RGT AR 680-31-9 HMPT

STAGE(3) RGT J 12125-02-9 NH4Cl SOL 7732-18-5 Water

PRO AO 263761-15-5, AP 321522-35-4

RCT AO 263761-15-5 RX(11) STAGE(1) RGT AT 1191-15-7 AlH(Bu-1)2 SOL .75-09-2 CH2C12

STAGE(2) RGT J 12125-02-9 NH4C1 SOL 67-56-1 MeOH, 7732-18-5 Water, 60-29-7 Et20

PRO AS 312492-69-6

RCT AU 187283-44-9 RX(12)

SN 10/563058 Page 81 of 172 STIC STN SEARCH RESULTS

VIELD 908

RCT AP 271792-03-1 RX (9)

RGT AQ 1070-89-9 (Me3Si)2N.Na SOL 109-99-9 THF STAGE(1)

STAGE(2) RCT AN 279226-92-5

PRO K 279226-93-6 NTE stereoselective

RCT J 279227-12-2

RX (2)

STAGE(1) RGT M 280-64-8 9-BBN SOL 109-99-9 THF

STAGE(2)

RCT K 279226-93-6 RGT N 534-17-8 G-25CO3, O 603-32-7 Ph3As CAT 51364-51-3 Ph2-pentadienone Pd G-25-2 DME

PRO L 279226-94-7

THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT stereoselective [: 25 NTE st REFERENCE COUNT:

L33 ANSWER 18 OF 23 CASREACT ACCESSION NUMBER: 134:1115 TITLE:

SREACT COPYRIGHT 2007 ACS on STN 134:115799 CASREAGT Full-text Process for the production of epothilone B and derivatives as well as intermediate products for this

process

Mulzer, Johann; Martin, Harry Schering Aktiengesellschaft, Germany PCT Int. Appl., 50 pp. INVENTOR(S): PATENT ASSIGNEE(S): SOURCE: 8

SN 10/563058 Page 82 of 172 STIC STN SEARCH RESULTS

CODEN: PIXXD2 Patent English FAMILY ACC. NUM. COUNT: PATENT INFORMATION: " DOCUMENT TYPE: LANGUAGE:

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APPLICATION NO.	!	WO 2000-US20064		BG,	FI,	8	Ĭ,	11,	₽,	TZ,	3	NE,	EP 2000-948907	II,		JP 2001-512523	2-30	9-14	2000-US20064		
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DATE		20010201	2001	AT,	ž	IL, IN, IS, JP,	Ř	SK,	Ϋ́Z	Ĭ,	F,	હ	2002	CH, DE, DK, ES, F	Ę,	20030212	20020321			PAT	
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PATENT NO.		2001007439	2001	3		HU, ID,				RW:			1226	æ.		JP 2003505459	NO 2002000308	PRIORITY APPLN. INFO.		OTHER SOURCE(S):	
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The present invention is directed to a process for the production of epothilone B compds., the improvement comprising preparing said compds. by cyclization of a compound produced from an intermediate of formula (I) wherein 9G is a protecting group. AB

RX(107) OF 190 COMPOSED OF RX(8), RX(19), RX(9), RX(10), RX(11), RX(12), + X + AU RX(13), RX(14)
AF + G + AJ + AN RX(107)

SN 10/563058 Page 79 of 172 STIC STN SEARCH RESULTS

CD 7553-56-2 I2

stereoselective CB 335160-07-1

CB 335160-07-1, BM 113453-27-3 CF 7440-66-6 Zn, CG 7440-50-8 Cu RX (32)

CE 335160-08-2

14221-01-3 Pd(PPh3)4 71-43-2 Benzene

stereoselective

CE 335160-08-2 AF 3144-16-9 10-CSA CI 335160-09-3

RX (33)

stereoselective Meon

79-37-8 (COC1)2, Z 67-68-5 DMSO CI 335160-09-3 F 79-37-8 (COC RGT PRO SOL NTE RX (34)

CJ 335160-10-6 75-09-2 CH2C12

RCT CJ 335160-10-6, AL 187283-45-0 stereoselective

RX (35)

STAGE(1)

RCT AM 69739-34-0 RGT AP 108-48-5 2,6-Lutidine STAGE (2)

STAGE (3) RGT AQ 584-08-7 K2CO3 SOL 67-56-1 M⊖OH

CK 335160-11-7

THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT NTE stereoselective REFERENCE COUNT: 19

SREACT COPYRIGHT 2007 ACS on STN 134:178371 CASREACT Full-text Synthesis and biological evaluation of highly potent ACCESSION NUMBER: 134:17

Altmann, K.-H.; Bold, G.; Caravatti, G.; Florsheimer, analogues of epothilones B and D

Novartis Pharma AG, TA Oncology Research, Basel,

CORPORATE SOURCE:

SOURCE:

AUTHOR(S):

TITLE:

Bioorganic & Medicinal Chemistry Latters (2000), CH-4002, Switz.

CODEN: BMCLE8; ISSN: 0960-894X

Elsevier Science Ltd

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

2

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the common intermediate and allows variation of the side-chain structure in a highly convergent and stereoselective manner. These epothilone analogs, e.g. are more potent inhibitors of cancer cell proliferation than the corresponding parent epothilones B or D.

2

RX(27) OF 370 COMPOSED OF RX(9), RX(2) RX(27) AP + AN + J ===> L

Ā

SN 10/563058 Page 77 of 172 STIC STN SEARCH RESULTS

CORPORATE SOURCE:

SOURCE:

DOCUMENT TYPE: LANGUAGE: GI

OODEN: 69AXZT Conference; (computer optical disk) English

Proceedings of ECSOC-3, [and] Proceedings of ECSOC-4, Sept. 1-30, 1999 and 2000 (2000), Meeting Date 1999-2000, 1431-1442. Editor(9): Pombo-Villar, Esteban. Molecular Diversity Preservation International: Basel, Switz.

Wartmann, Markus; Altmann, Karl-Heinz TA Oncology Research, Novartis Pharma AG, Basel, CH-4002, Switz.

The authors have synthesized epothilone analogs, e.g. I, with modifications in the northern hemisphere and the heterocyclic side-chain. In all three cases the key steps for construction of the macrocyclic skeleton involve Yamaquehi macrolactonization, the build-up of the requisite seco-acid through aldol reaction between the C7-C15 aldehyde and the diamion of the O-protected C1-C6 β-hydroxy acid fragment, and the assembly of the C7-C15 aldehyde through the appropriate type of Pd(0)-catalyzed coupling reaction. The IC50 for growth inhibition of the KB-31 tumor cell line for I was 0.45 nM.

9

RX(284) OF 370 COMPOSED OF RX(29), RX(30), RX(31), RX(32), RX(33), RX(34),

\=== RX(35) Y + BX + BM + AL + AM RX (284)

, (CH2) 3 ✓I

SN 10/563058 Page 78 of 172 STIC STN SEARCH RESULTS

RX (30)

STAGE(2)

 \mathcal{L}

SN 10/563058 Page 75 of 172 STIC STN SEARCH RESULTS

A highly convergent total synthesis of the natural products epothilone B and is described. The route is highlighted by efficiant generation of a C12-C13 triaubstituted olefin I which exploits a sequential Nozaki-Hiyama-Kishi coupling and a stereossalective thionyl chloride rearrangement.

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RX(53) OF 175 COMPOSED OF RX(6), RX(7), RX(13), RX(14) RX(53). O + N ===> AN

SN 10/563058 Page 76 of 172 STIC STN SEARCH RESULTS

PAGE 1-A

PAGE 1-B

AN YIELD 83%

7719-09-7 SOC12 355009-08-4 o 355009-06-2 U 7719-09-7 SO RCT RGT PRO SOL RX (6)

60-29-7 Et20, 109-66-0 Pentune

Y 22560-16-3 Superhydride X 210690-99-6 T 355009-08-4 RGT PRO SOL NTE

RX (7)

other product detected 109-99-9 THF

RX(13)

X 210690-99-6 AC 26299-14-9 PCC ' AM 193146-27-9 RGT PRO

N 187527-25-9, AM 193146-27-9 AO 4111-54-0 LiN(Pr-1)2 AN 193146-49-5 RX (14)

stereoselective, other product detected, no exptl.
37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT RCT N RGT AO PRO AN NTE ST REFERENCE

CASREACT L33 ANSWER 16 OF 23 ACCESSION NUMBER: TITLE:

SREACT COPYRIGHT 2007 ACS on STN
134:311010 CASREACT Full-text
Synthetic epothilone analogs with modifications in the northern hemisphere and the heterocyclic side-chair-synthesis and biological evaluation End, Nicole; Bold, Guido; Ceravatti, Glorgio;

AUTHOR(S):

72

PRO AM 298702-16-6

SN 10/563058 Page 73 of 172 STIC STIN SEARCH RESULTS

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NTE STEREOSELECTIVE

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STACE(1)
RGT AS 7647-01-0 HCl
CAT 109361-17-3 Ruthenlum, bis[(IR)-[1,1'-binaphthalene]-2,2'-
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   Department of Chemistry & Biochemistry, University of Notre Dame, Notre Dame, IN, 46556-5670, USA
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   Organic Letters (2001), 3(14), 2221-2224

CODEN: ORLEF7; ISSN: 1523-7060

American Chemical Society
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     135:180642 CASREACT Full-text
Total Synthesis of Epothilones B.and D
                                                                                                                                                                                                                                                                                                                                             diylbis[diphenylphosphine-KP]]di-µ-chlorodichloro(N,N-diethylethanamine)di-SOL 67-56-1 MeOH
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 COPYRIGHT 2007 ACS on STN
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   Taylor, Richard E.; Chen, Yue
                                                                                                                                                                                                                                                              RCT AR 298702-17-7, AT 67-56-1
                                                                                                         STAGE(2)
RGT N 144-55-8 NaHCO3
                                                                                                                                                                                                                                                                                                                                                                                                                                                                        STAGE(3)
RGT N 144-55-8 NaHCO3
                                     STAGE(1)
RGT AS 7647-01-0 HCl
SOL 67-56-1 MeOH
                                                                                                                                                                                                                                                                                                                                                                                                                        STAGE(2)
RGT AV 1333-74-0 H2
                                                                                                                                                           STAGE(3)
SOL 75-09-2 CHZC12
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            STAGE(4)
SOL 75-09-2 CH2C12
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           English
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             L33 ANSWER 15 OF 23 CASREACT
ACCESSION NUMBER: 135:18
                                                                                                                                                                                                          PRO AR 298702-17-7
NTE STEREOSELECTIVE
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NTE STEREOSELECTIVE
RCT AM 298702-16-6
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CORPORATE SOURCE:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     PUBLISHER:
DOCUMENT TYPE:
LANGUAGE:
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       SOURCE:
                                                                                                                                                                                                                                                                RX(10)
     RX (9)
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            RCT AB 298702-07-5
RGT AO 603-32-7 Ph3As, AP 534-17-8 Cs2C03
CAT 72287-26-4 Palladium, [1,1'-bis(diphenylphosphino-
                                                     PAGE 1-B
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                κP) ferrocene]dichloro-, (SP-4-2)-
SOL 68-12-2 DMF
                                                                                                                                                                                                                                                                                                                                                                                                                                   STAGE(3)
RGT AE 1070-89-9 (Me3Si)2N.Na
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          RGT AN 280-64-8 9-BBN SOL 109-99-9 THF
                                                                                                                                                                                                                                                                                                         RGT AC 109-72-8 BuLi
SOL 109-99-9 THF
                                                                                                                                                                                                                                                                                                                                                             STAGE(2)
RGT AD 7553-56-2 I2
SOL 109-99-9 THF
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      STAGE(3)
SOL 7732-18-5 Water
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 STAGE(4)
RCT AA 298702-12-2
SOL 109-99-9 THF
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     STAGE(5)
RGT D 64-19-7 AcOH
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       STAGE(4)
SOL 60-29-7 Et20
                                                                                                                                                                                                                                          RCT Z 4736-60-1
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STEREOSELECTIVE
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                                                                                                                                                        AU
YIELD 42%
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            RX (8)
                                                                                                                                                                                                                                                            RX (6)
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SN 10/563058 Page 71 of 172 STIC STN SEARCH RESULTS

ACCESSION NUMBER: 135:226826 CASREACT Full-text
TITLE: Synthesis of epothliones, intermediates and analogs for use in treatment of cancers with multidrug resistant phenotype
INVENTOR(S): Stachel, Shawn; Chou, Ting-chao DOCUMENT TYPE: POT Int. Appl., 234 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
ENGINEE: Patent
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

多最早男子 i i ď 20010301 20010301 , NL, SE, MC, E CH, LLS, UZ, 유 도 교 ER, BE, SE, TG 20010301 20010301 G. F. K. B. B. AT, PT, TD, FR, GB, GR, IT, LI, LU, MK, CY, AL, TR SK, SK JP 2001-563492 US 2000-185968P US 2000-250447P WO 2001-US6643 CA 2001-2401800 EP 2001-916335 APPLICATION NO. WO 2001-US6643 8 K B ă, ș, š, Ą SE, TW, KG, MARPAT 135:226826 数 3 8 8 € 5 8.8.8 ES, RO, 20010907 SE, YE, SE, 20021127 £ 8 5 20010907 DATE EI, SK, MG, FR, E & EI, DE, 3 SI, ដ KIND ¥ BE, CH, SI, LT, ខ្ល JP 2004500388 PRIORITY APPLN. INFO.: λΕ, ΑĞ, CR, CC, R: AT, BE, WO 2001064650 WO 2001064650 **克里岛为黑** OTHER SOURCE(S): CA 2401800 EP 1259490 E, PATENT NO. **RW:**

AB The present invention provides convergent processes for preparing epothilones, descayepothilones, and analogs, e.g., I (M = NH, O; CY = aryl, heteroaryl; q = 1-5; W = absent, NH, ∞ , CS, O, S, C(V)2; V = H, halogen, OH, SH, amino, (un)substituted alkyl, heteroalkyl, aryl, heteroaryl; m = 1-5; bond W···Rl =

SN 10/563058 Page 72 of 172 STIC STN SEARCH RESULTS

single bond, double bond; R1 = OR, SR, NR2; CO2R, CONH, N3, N2, NZR; halogen, un(substituted) cyclic or acyclic aliphatic, heteroaliph., aryl or heteroaryl, polymer, carbohydrate; R = H, un(substituted) cyclic or acyclic aliphatic, heteroaliph., aryl or heteroaryl, protecting group; R2, R3 = H, un(substituted) aliphatic, heteroaryl, protecting group; R2, R3 = H, un(substituted) aliphatic, heteroaryl, acyl, acyl, arcyl, heteroaryl, acyl, aryl or heteroaryl, acyl, aryl, heteroaryl, acyl, arcyl, acyl, alkoxy, carboxy, carboxyl, optionally substituted by one or more of OH, alkoxy, carboxy, carboxyl, N3, N2, N3R, cyclic or acyclic aliphatic, aryl, heteroaryl, 2 = O, N(ORE), NNFRG; RE, RF, RG = un(substituted) cyclic or acyclic aliphatic; n = O-31, for the troatment of cancer aliphatic, aryl, heteroaryl; Z = O, N(ORE), NNFRG; RE, RF, RG = un(substituted) cyclic or acyclic aliphatic; n = O-31, for the troatment of cancer and cancer which has developed a multi-drug phenotype are presented. Thus, 21-oxo-12,13-deaty-pothilone B and 15-azaepothilone B were active vs leakenia CCRF-CEM cells (ICSO = O.027 µM; ICSO = O.021 µM, resp.).

RX(112) OF 295 COMPOSED OF RX(8), RX(8), RX(9), RX(10) RX(112) Z + AA + AL + AL = AT = AD

SN 10/563058 Page 69 of 172 STIC STN SEARCH RESULTS

Preparation of epothilone intermediates Vite, Gregory D.; Kim, Soong-Hoon; Hoeefle, Gerhard Bristol-Myers Squibb Company, USA 135:287591 CASREACT Full-text PCT Int. Appl., 28 pp. CODEN: PIXXD2 Patent INVENTOR(S): PATENT ASSIGNEE(S): SOURCE: ACCESSION NUMBER:

DOCUMENT TYPE:

English

FAMILY ACC. NUM. COUNT: PATENT INFORMATION: LANGUAGE:

CA, CH, CM, GK, GE, GH, CM, LK, LR, LS, YE, PT, RO, UG, UZ, UZ, AT, BE, CH, CY, PT, SE, TR, BF, 20010319 20030528 20010323 20000324 DATE SW, US 2003-447082 US 2000-191975P US 2001-811808 APPLICATION NO. WO 2001-US9620 US 2001-811808 FI's FR, GB, CI's CM, GA, A1 20020411 20030715 ¥,¥ 20011004 AL, AM, AT, CU, CZ. PP KIND DATE US 2002042109
US 6593115
US 2004023345
PRIORITY APPLN. INFO.: WO 2001073103 PATENT NO. **RW:**

MARPAT 135:287591 OTHER SOURCE(S):

20010319

containing a carboxyl group which is esterified, the hydroxyl groups on the moiety protected and the resulting compound oxidized by, e.g. ozone, to form a first intermediate. The first intermediate can be reacted with a enzymically degrading certain epothilone compds, to form ring-open structures The present invention relates to a process for the preparation of intermediates useful in the synthesis of epothilone analogs by initially triphenylphosphine adduct to yield a compound containi position 1 which is subsequently hydrolyzed to form a Æ

: G Vitit ii 4 + O... RX(4) OF 31

SN 10/563058 Page 70 of 172 STIC STN SEARCH RESULTS

OMe

PIELD 558

RCT 0 190369-98-3 RX (4)

STAGE (1)

RGT R 1070-89-9 (Me3Si) 2N.Na SOL 109-99-9 THF RCT P 364336-83-4 SOL 109-99-9 THF STAGE(2)

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PRO Q 364336-77-6

L33 ANSWER 14 OF 23 CASREACT COPYRIGHT 2007 ACS on STN

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EP 868

RCT AB 370578-43-1 RX (6) STAGE(1) RGT AD 121-44-8 Et3N SOL 75-09-2 CH2C12

RGT AE 7719-09-7 SOC12 SOL 75-09-2 CH2C12 STAGE(2)

STAGE(3) RGT G 7732-18-5 Water

STAGE(4) RGT AF 429-41-4 Bu4N.F SOL 109-99-9 THF

PRO AC 370578-22-6 . NTE stereoselective

RCT AC 370578-22-6, EM 994-30-9

RX (64)

RGT AD 121-44-8 Et3N CAT 1122-58-3 4-DMAP SOL 75-09-2 CH2C12 STAGE (1)

RGT D 144-55-8 NAHCO3 SOL 7732-18-5 Water STAGE(2)

PRO DL 370578-62-4

RCT DL 370578-62-4

RX (32)

STAGE (1)

SN 10/563058 Page 68 of 172 STIC STN SEARCH RESULTS

RGT CK 7529-22-8 Me-morpholineoxide SOL 75-65-0 t-BuOH, 109-99-9 THF, 7732-18-5 Water

STAGE(2) CAT 20816-12-0 0504 SOL 7732-18-5 Water

STAGE(3) RGT DN 7631-90-5 NaHSO3

STAGE(4) RGT DO 546-67-8 Pb(OAc)4 SOL 141-78-6 ACOEt

PRO DM 342607-03-8

DQ 219990-08-6 RCI RX (33)

STAGE(1) RGT AU 4111-54-0 LiN(Pr-i)2 SOL 109-99-9 THF

RCT DM 342607-03-8 SOL 109-99-9 THE STAGE(2)

STAGE (3)

NGE (3) RGT AA 12125-02-9 NH4C1 SOL 7732-18-5 Water

DR 342607-02-7 in-situ generated reagent, stereoselective

DR 342607-02-7, FO 17341-93-4 E 110-86-1 Pyridine EO 342607-17-4 75-09-2 CHZC12 RCT RGT PRO SOL RX (66)

RCT E0 342607-17-4 RX (45)

STAGE(1)
RGT CK 7529-22-8 Me-morpholineoxide .
SOL 75-65-0 t-BuOH, 109-99-9 THF, 7732-18-5 Water

STAGE(2) CAT 20816-12-0 0s04

RGT DN 7631-90-5 NaHSO3

STAGE (3)

STAGE(4) RGT DO 546-67-8 Pb(0Ac)4 SOL 141-78-6 AcOEt

THERE ARE 99 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT PRO EP 342607-35-6 66 REFERENCE COUNT:

L33 ANSWER 13 OF 23 CASREACT COPYRIGHT 2007 ACS on STN

SN 10/563058 Page 65 of 172 STIC STN SEARCH RESULTS

RGT Z 109-72-8 BuLi SOL 109-99-9 THF STAGE(2)

STAGE(3) RGT CJ 37342-97-5 Hydrozirconocene Cl SOL 109-99-9 THF

STAGE (4)

RGT CK 7553-56-2 I2 SOL 109-99-9 THF

CH 335160-07-1 PRO

RCT AO 113453-27-3, CH 335160-07-1 RX (30)

CM 12621-78-2 Zinc alloy, base, Zn,Cu 14221-01-3 Pd(PPh3)4 71-43-2 Benzene STAGE (1)

Sol

STAGE(2) RGT BY 3144-16-9 10-CSA SOL 67-56-1 MeOH

STAGE(3)

RGT BL 67-68-5 DMSO, AB 79-37-8 (CCC1)2 SOL 75-09-2:GH2C12

PRO CL 335160-10-6

RCT H 187283-45-0, CL 335160-10-6 RX(31)

STAGE(1) RGT BT 4111-54-0 Lin(Pr-i)2

STAGE(2)

RCT F 69739-34-0 RGT BW 108-48-5 2,6-Lutidine

AGE (3) RGT CQ 584-08-7 K2CO3 SOL 67-56-1 MaOH STAGE (3)

PRO CP REFERENCE COUNT:

THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT CP 335160-11-7

CASREACT L33 ANSWER 12 OF 23 ACCESSION NUMBER:

TITLE:

AUTHOR(S): CORPORATE SOURCE:

COPYRIGHT 2007 ACS on STN

135:331283 CASREACT Full-text
Stereoselective Syntheses of Epothilones A and B via
Nitrile oxide Cycloadditions and Related Studies
Mode, Jeffrey W.; Carreira, Erick M.
Laboratorium fuer Organische Chemie, ETH-Zuerich,

Zurich, CH-8092, Switz.
Journal of Organic Chemistry (2001), 66(19), 6410-6424
CODEN: JOCEAH; ISSN: 0022-3263

American Chemical Society

Journal

PUBLISHER: DOCUMENT TYPE:

SOURCE:

65

SN 10/563058 Page 66 of 172 STIC STN SEARCH RESULTS English

LANGUAGE: GI

The expedient and fully stereocontrolled synthesis of epothilones A (I; R = H) and B I (R = Me) are described. The routes described make extensive study of nitrile oxide cycloaddns. as surrogates for aldol addition reactions and have led to the realization of a highly convergent synthesis based on the Kanemasa hydroxyl-directed nitrile oxide cycloaddn. As well, our synthetic efforts have led to the development of new reaction methodologies and served as the proving ground for several modern methods for asym. carbon-carbon bond

9

RX(451) OF 751 COMPOSED OF RX(6), RX(64), RX(32), RX(33), RX(66), RX(45) RX(451). AB + EM + DQ + FO ===> EP

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SN 10/563058 Page 63 of 172 STIC STN SEARCH RESULTS

SOL 109-99-9 THF

BR 186692-68-2 stereoselective

RX (28)

AX 461044-35-9, BR 186692-68-2 BW 603-32-7 Ph3As, BX 534-17-8 Cs2CO3, BY 280-64-8 9-BBN BV 461044-42-8 RGT PRO CAT

72287-26-4 Palladium, [1,1'-bis(diphenylphosphino-

kP)ferrocene]dichloro-, (SP-4-2)stereoselective, regioselective

1. THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS
T. RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT REFERENCE COUNT:

CASREACT L33 ANSWER 11 OF 23 ACCESSION NUMBER: TITLE:

SREACT COPYRIGHT 2007 ACS on STN 136:318824 CASRRACT Pull-text Synthetic and semisynthetic analogs of epothilones: chemistry and biological activity Altmann, Karl-Heinz; Blommers, Marcel J. 3.; Caravetti, Giorgio; Florsheimer, Andreas; Nicoleou, Kyriacos C.; O'Reilly, Terrenes; Schmidt, Alfred;

AUTHOR(S):

TA Oncology Research, Novartis Pharma AG, Basel, Schinzer, Dieter; Wartmann, Markus

CH-4002, Switz. CORPORATE SOURCE:

ACS Symposium Series (2001), 796(Anticancer Agents), 112-130

SOURCE:

CODEN: ACSMC8; ISSN: 0097-6156 American Chemical Society

this paper we present the synthesis of these analogs and we discuss the impact of such modifications on tubulin polymerization activity as well as vivo, we have investigated a series of structural modifications involving the epoxide site (C12/C13) and the heterocyclic side-chain of epothilones. In which exhibit potent in vitro antiproliferative activity. Epothilone B is a 3 30-fold more potent inhibitor of human cancer cell growth than paclitaxel in paclitaxel-sensitive cancer cell lines and in paclitaxel-reasistant lines exceeds paclitaxel activity by 102 - 103-fold. In addition, epothilone B models. In order to gain a better understanding of the structural requirements for epothilone-mediated cytotoxicity and antitumor activity and Epothilones A and B are naturally occurring microtubule depolymn. inhibitors, to discover analogs with similar potency but perhaps better tolerability in cytotoxicity in vitro. PUBLISHER: DOCUMENT TYPE: LANGUAGE: AB Epothilones

RX(146) OF 320 COMPOSED OF RX(29), RX(30), RX(31) RX(146) BK + CG + AC + H + F ===> CP

SN 10/563058 Page 64 of 172 STIC STN SEARCH RESULTS

RCT BK 188730-08-7, CG 558-13-4 RX (29)

SN 10/563058 Page 61 of 172 STIC STN SEARCH RESULTS

of novel pyranose synthons. The utility of this very convergent and effective propenyl)-L-xylonic acid 6-lactone. This compound was a chiral synthon needed for the total synthesis of epothilons C [(48,7R,88,98,13Z,168)-4,8-dihydroxy-5,5,7,9-tetramethyl-16-[(1E)-1-methyl-2-(2-methyl-4method is demonstrated by the concise total synthesis of epothiones. The stereosalective I-catalyzed aldol condensation of acetaldehyde with (25)-3-hydroxy-2-methylpropanal gave 2,4-dideoxy-4-methyl-L-erythro-pentopyranose. Oxidation of the latter gave 2,4-dideoxy-4-methyl-L-threo-pentonic acid 6-lactone. Alkylation of the 6-lactone gave 2,4-dideoxy-4-methyl-2-(2thiazoly1)etheny1]oxacyclohexadec-13-ene-2,6-dione

RX(172) OF 316 COMPOSED OF RX(23), RX(24), RX(25), RX(27), RX(28) RX(172) BC + BH + BN + BQ + AX ===> BV

SN 10/563058 Page 62 of 172 STIC STN SEARCH RESULTS

BV YIELD 65% -ngo-t

PAGE 1-B

BF 109-63-7 BF3-Et20 BE 461044-38-2 BC 247900-97-6 RX (23)

7732-18-5 Water, 75-05-8 MeCN RX (24)

BE 461044-38-2, BH 109-80-8 BI 461044-39-3 7550-45-0 TiCl4 RCT PRO CAT

BI 461044-39-3 BL 79-37-8 (COCL)2, BM 67-68-5 DMSO BK 461044-40-6 RGT PRO PRO RX(25)

BK 461044-40-6, BN 184246-51-3 AR 109-72-8 BuLi BO 461044-41-7 RCT RGT PRO SOL RX (26)

stereoselective

BO 461044-41-7 RCT RX(27)

RGT BS 7616-83-3 Hg(ClO4)2, BT 471-34-1 CaCO3 SOL 109-99-9 THF, 7732-18-5 Water STAGE (1).

STAGE(2) RCT BQ 29949-93-7 RGT V 680-31-9 HMPT, BU 1070-89-9 (Me3Si)2N.Na

SN 10/563058 Page 59 of 172 STIC STN SEARCH RESULTS

OON SUBSTAGE(1) room temperature -> -75 deg C SUBSTAGE(2) 30 minutes SUBSTAGE(3) 1 hour, -75 deg C SUBSTAGE(4) 1 hour, room temperature

L 335160-06-0

RCT

RX (3)

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PAGE 1-B

BU YIELD 63% 1 OMe

SUBSTAGE(1) 10 minutes, 18 - 23 deg C SUBSTAGE(2)·1 hour, room temperature BF 188730-08-7, BH 558-13-4 BJ 603-35-0 PPh3 335160-05-9 75-09-2 CH2C12 RGT PRO SOL SOL RX(18)

L 335160-06-0 109-99-9 THF, 110-54-3 Hexane BI 335160-05-9 AJ 109-72-8 BuLi RGT PRO SOL RX(19)

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THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT
                                                                                                                                                                                                                                                                                                                                                                                                                           DC 603-32-7 Ph3As, DD 534-17-8 Cs2CO3 72287-26-4 Palladium, [1,1'-bis(diphenylphosphino-
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     SUBSTAGE(1) room temperature -> -10 deg C
SUBSTAGE(2) -10 deg C -> room temperature
SUBSTAGE(3) 24 hours, room temperature
             RGT N 37342-97-5 Hydrozirconocene Cl
SOL 109-99-9 THF
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 30 minutes, room temperature
                                                                                                                         O 7553-56-2 12
SUBSTAGE(1) 10 minutes, 20 - 25 deg C
SUBSTAGE(2) 10 minutes
                                                                                                                                                                                                                                                                                                                                                                                                                                                                KP) ferrocene]dichloro-, (SP-4-2)-7732-18-5 Water, 68-12-2 DMF
                                                                                                                                                                                                                                                                                                                                                      4 hours, room temperature
                                                                                                                                                                                                                                                                                                                 DB 280-64-8 9-BBN
                                                                                                                                                                                                                                                                                                                                                                                                            M 335160-07-1
                                                                                                                                                                                                                                                                                                                                    109-99-9 THF
                                                                                                                                                                                                                      stereoselective
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                BU 501691-10-7
                                                                                                                                                                                                                                                           RCT CW 279227-12-2
                                                                                                                                                                                               PRO M 335160-07-1
NTE stereoselectiv
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  20
                                                                                                            STAGE (2)
STAGE (1)
                                                                                                                                                                                                                                                                                                STAGE (1)
                                                                                                                                                                                                                                                                                                                                                                                          STAGE (2)
                                                                                                                           8 RG T
                                                                                                                                                                                                                                                                                                                 SOL
SOL
SOL
                                                                                                                                                                                                                                                                                                                                                                                                            RGT CAT
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     SOL
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                PRO BU
REFERENCE COUNT:
                                                                                                                                                                                                                                                           RX (39)
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Enzymic reactions catalyzed by DERA (2-deoxyribose-5-phosphate aldolase, deoxyriboaldolase, (1)) provide the basis for a new strategy for the synthesis DOCUMENT TYPE: LANGUAGE: B

41(8), 1404-1407 CODEN: ACIEF5; ISSN: 1433-7651 Wiley-VCH Verlag GmbH

PUBLI SHER:

SOURCE:

137:247231 CASREACT <u>Full-text</u>
Aldolass-catalyzed asymmetric synthesis of novel pythonose synthons as a new entry to heterocycles and epothilones

CASREACT . COPYRIGHT 2007 ACS on STN

L33 ANSWER 10 OF 23 ACCESSION NUMBER:

TITLE:

Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA Angewandte Chemie, International Edition (2002),

Liu, Junjie; Wong, Chi-Huey

AUTHOR(S): CORPORATE SOURCE:

BO YIELD 93%

RCT T 193146-30-4D RX (27)

15 minutes, room temperature BY 1070-89-9 (Me3Si)2N.Na 109-99-9 THF STAGE(1) RGT B SOL 1

2

RCT BP 346652-91-3 CON 15 minutes, -78 deg C -> -40 deg C STAGE (2)

PRO BQ 583829-96-3 NTE solid-supported reaction REFERENCE COUNT: RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT

138:237914 CASREACT Full-text The total synthesis and biological assessment of CASREACT COPYRIGHT 2007 ACS on STN L33 ANSWER 9 OF 23 ACCESSION NUMBER: TITLE:

trans-epothilone A Altmann, Karl-Heinz; Bold, Guido; Caravatti, Giorgio; Denni, Donatienne; Florsheimer, Andreas; Schmidt, Alfred; Rihs, Grety; Wartmann, Markus Corporate Research, Novartis Pharma AG, Switz. Helvetica Chimica Acta (2002), 85(11), 4086-4110 CODEN: HCACAV; ISSN: 0018-019X Vorlag Helvetica Chimica Acta Journal CORPORATE SOURCE:

AUTHOR(S):

SOURCE:

English PUBLISHER: DOCUMENT TYPE: LANGUAGE:

SN 10/563058 Page 58 of 172 STIC STN SEARCH RESULTS

two different convergent strategies. In a first-generation approach, construction of the C(II)-C(I2) bond by Pdo-catalyzed Negishi-type coupling between the C(I2)-to-C(I3) trans-vinyl iodide II and the C(7)-to-C(I1) alkyl iodide III preceded the (nonselective) formation of the C(6)-C(7) bond by aldol reaction between the C(7)-to-C(I5) aldehyde and the dianion derived from the C(I)-to-C(I5) aldehyde and the dianion derived from the C(I)-to-C(I6), acid IV. The lack of selectivity, in the aldol step was addressed in a second-generation approach, which involved construction of the C(6)-C(7) bond in a highly diastereoselective fashion through reaction between The total synthesis of (125,135)-trans-epothilone A (1) was achieved based on cancer cell lines in vitro. In contrast, the biol. activity of V is at least two orders of magnitude lower than that of VI or I. the acetonide-protected C(1)-to-C(6) diol ("Schinzer's ketone") and the C(7)-to-C(11) aldehyde. As part of this strategy, the C(11)-C(12) bond was established subsequent to the critical aldol step and was based on B-alkyl Suzuki coupling between the C(1)-to-C(11) fragment and C(12)-to-C(15) transvinyl iodide II. Both approaches converged at the stage of the 3-0, 7-0-bis epoxidn. of the trans C(12)-C(13) bond could be achieved by epoxidn. with Oxone in the presence of the catalyst 1,2:4,5-di-0-isopropylidene-L-erythro-TBS-protected seco acid, which was converted to trans-deoxyepothilone A via Yamaguchi macrolactonization and subsequent deprotection. Stereoselective I is at least equipotent with natural epothilone A (VI) in its ability to induce tubulin polymerization and to inhibit the growth of human (12R,13R)-epoxide isomer (V) in 27% yield (54% based on recovered starting 2,3-hexodiuro-2,6-pyranose, which provided a 8:1 mixture of I and its The absolute configuration of I was established by X-ray

RX(123) OF 496 COMPOSED OF RX(18), RX(19), RX(3), RX(39) RX(123) BF + BH + CM ===> BU

25

SN 10/563058 Page 55 of 172 STIC STN SEARCH RESULTS

RGT CF 280-64-8 9-BBN SOL 109-99-9 THE SOL SUBSTAGE(1) From temperature SUBSTAGE(2) 3 hours, room temperature

STAGE(2) RGT E 7732-18-5 Water CON room temperature STAGE(3)
RCT CA 186692-68-2
RCT CA 186692-68-2
RCT T2287-26-4 Palladium, [1,1'-bis (diphenylphosphino-kP) ferrocene]dichloro-, (SP-4-2)SOL 68-12-2 DMF
CON SUBSTAGE(1) room temperature

SUBSTAGE(1) room temperature SUBSTAGE(2) 2 minutes, room temperature SUBSTAGE(3) room temperature SUBSTAGE(4) 8 hours, room temperature

STAGE(4)
RGT BS 12125-02-9 NH4C1
SOL 7732-18-5 Water
CON room temperature

PRO CE 461044-42-8

L33 ANSWER 8 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:
139:197285 CASREACT Full-text
TITLE:
A total synthesis of epothilones using solid-supported reagents and scavengers
AUTHOR(S):
Storer, R. Ian; Takemoto, Toshiyasu; Jackson, Philip
CORPORATE SOURCE:
University Chemical Laboratories, University of Cambridge, C

HO HO HO

SN 10/563058 Page 56 of 172 STIC STN SEARCH RESULTS

AB A total synthesis of epothilone C (I) with concomitant formal synthesis of epothilone A is described, using immobilized reagents and scavengers to effect multistep synthetic transformations and purifications.

RX(27) OF 210 ... T + BP ===> BQ.

T solid supporte d

BP

PAGE 1-A

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STEPS

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PAGE 1-B
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RCT AG 247900-97-6, AI 109-80-8 RX (9)

CE YIELD 65% → OBu-t

SOL 75-09-2 CH2C12
SOL 75-09-2 CH2C12
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) room temperature
SUBSTAGE(4) 30 minutes STAGE(1)

RGT J 144-55-8 NaHCO3 SOL 7732-18-5 Water STAGE (2)

PRO AJ 461044-39-3

RX (25)

STAGE (1)

SN 10/563058 Page 54 of 172 STIC STN SEARCH RESULTS

KGT BV 79-37-8 (CCL1)2 SOL 75-09-2 CH2C12, 67-68-5 DMSO CON SUBSTAGE(2) 30 minutes

STAGE(2) RCT AJ 461044-39-3 SOL 75-09-2 CH2C12 CON SUBSTAGE(2). 3 hours

STAGE(3) RGT AE 121-44-8 Et3N

PRO. BU 461044-40-6

RCT BX 184246-51-3 RX (26)

RGT BF 109-72-8 BuLi SOL 109-99-9 THF CON SUBSTAGE(2) 15 minutes STAGE(1)

RCT BU 461044-40-6 CON SUBSTAGE(2) room temperature

STAGE(3) RGT BS 12125-02-9 NH4Cl SOL 7732-18-5 Water

PRO BY 461044-41-7

RCT BY 461044-41-7 RX (27)

SOL 7732-18-5 Water
CON SUBSTAGE(1) room temperature
SUBSTAGE(2) 2 hours, room temperature STAGE(1)

STAGE(2)
SOL -60-29-7 Et20
CON SUBSTAGE(1) room temperature
'SUBSTAGE(2) 10 minutes, room temperature

, 2020-28-8 BG 680-31-9 HMPT, CD 1070-89-9 (Me351)2N.Na 109-99-9 THE SUBSTAGE(3) room temperature SUBSTAGE(4) hour SOL

STAGE(4) RGT BS 12125-02-9 NH4Cl SOL 7732-18-5 Water

PRO CA 186692-68-2

RCT BT 461044-35-9

RX(28)

STAGE(1)

S

5

3 £ £ £ 9 E 8 7 8

BY, FI, KR,

KG,

¥25,8,¥

AZ, DM, IS,

BB, EC,

¥ S

₹,9,

AE, AG, GR, CR, LT, LT,

ĕ,₹ ES,

SN 10/563058 Page 51 of 172 STIC STN SEARCH RESULTS

RCT . AS 863981-49-1 RX(14)

AU 64-17-5 EtOH 24057-28-1 Pyridinium tosylate 64-17-5 EtOH 65 deg C STAGE(1) SOL SOL

Q 79-37-8 (COC1)2, AV 67-68-5 DMSO 75-09-2 CH2C12 STAGE (2) SOL SOL SOL

-78 deg C

AW 121-44-8 Et3N -78 deg C -> room temperature STAGE (3) 8 S N S N

AT 688318-68-5 Swern oxidn. in stage 2 PRO

RCT AY 185148-95-2

RX (15)

RGT BA 4111-54-0 LiN(Pr-i)2 CON -78 deg C STAGE(1)

AT 688318-68-5 STAGE(2) RCT AT 680318-6 CON -78 deg C

PRO AZ 688318-69-6

THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT stereoselective NTE ST REFERENCE COUNT:

EACT COPYRIGHT 2007 ACS on STN 139:277113 CASREACT Full-text L33 ANSWER 7 OF 23 CASREACT ACCESSION NUMBER: 139: TITLE:

Synthesis of atorvastain and epothilone synthons via 2-deoxyribose-5-phosphate aldolase-catalyzed ssymmetric aldol condensation of aldehydes Wong, Chi-huey; Liu, Junjie; De Santis, Grace; Burk,

The Scripps Research Institute, USA; Diversa Mark

PCT Int. Appl., 63 pp CODEN: PIXXD2 Corporation PATENT ASSIGNEE (S):

INVENTOR(S):

SOURCE:

English Patent DOCUMENT TYPE:

LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

BZ, GB, GB, KZ, LC, NO, NZ, 20030314 DATE APPLICATION NO. WO 2003-US7982 20040401 AT, AU, DE, DK, IL, IN, MA, MD, 1 20030925 DATE KIND WO 2003077868 WO 2003077868 PATENT NO.

STIC STN SEARCH RESULTS SN 10/563058 Page 52 of 172

12, BY, ES, TR, PT, TT, AZ, EE, SK, SK, 20060705 Т. 0030314 GB, GR, IT, LI, LU, NL, SE, CY, AL, TR, BC, CZ, EE, HU, 20030314 20030314 Ž, ÄΥ US 2006-481653 US 2002-364641P US 2003-390544 WO 2003-US7982 AU 2003-225810 US 2003-390544 EP 2003-744689 JP 2003-575922 SK, SL, 1J, ZM, ZW ű SE, YU, YU, AT, IT, GA, Ж, Ў, 20031218 20041215 DK, ES, FI, RO, 20050714 SD, 20030929 20070118 ŠĆŠĆ ¥ČČŠĆ 급물 UA, UG, US, UZ, V GH, GM, KE, LS, N KG, KZ, MD, RU, 1 FI, FR, GB, GR, H BF, BJ, CF, CG, C CH, CE, 1 Y, JP 2005520510 US 2007015260 PRIORITY APPLIN. INFO.: £,5,5, CA 2479247 AU 2003225810 US 2003232416 EP 1485498 R: AT RW:

MARPAT 139:277113 OTHER SOURCE(S):

acceptor aldehydes. The reaction products typically contain at least two new stereogenic centers and can be produced in enantionerically pure form. As such, DERA catalyzed asym. aldol chemical can be exploited to produce synthons for the synthesis of a variety of bioactive mols., e.g. epothilone A. catalyze sequential asym. aldol reactions between a wide variety of donor and phosphate aldolase (DERA, EC 4.1.2.4) and variants thereof can be used to The present invention is based on the discovery that 2-deoxyribose-5-2

RX(147) OF 294 COMPOSED OF RX(9), RX(25), RX(26), RX(27), RX(28) RX(147) AG + AI + BX + BZ + BT ===> CE

SN 10/563058 Page 49 of 172 STIC STN SEARCH RESULTS

В

An efficient synthesis of the epothilone B derivative.26-fluoroepothilone B (I) was realized by early introduction of the synthetically demanding fluoromethyl epoxide function. The presence of a fluoro substituent results in a remarkable increase in the stability of the epoxide, which tolerates the wide range of reaction conditions required for the fragment coupling step and each game transformations.

RX(175) OF 310 COMPOSED OF RX(10), RX(24), RX(25), RX(26), RX(27), RX(14),

RX(15)

RX(175) H + AG + BW + AY ===> AE

STEPS

SN 10/563058 Page 50 of 172 STIC STN SEARCH RESULTS

AZ YIELD 778

RX (24)

3

RX (25)

4

SN 10/563058 Page 47 of 172 STIC STN SEARCH RESULTS

EI YIELD 938

SN 10/563058 Page 48 of 172 STIC STN SEARCH RESULTS

```
SUBSTAGE(1) room temperature
SUBSTAGE(2) 18 hours, 90 deg C
SUBSTAGE(3) 90 deg C -> room temperature
attachment to solid-supported reagent Fluka polymer bound triphenylphosphine
                                                                                                                                                                           CY 1070-89-9 (Me3Si)2N.Na
109-99-9 THF
N 193146-30-4
O 603-35-0D PPh3
EB 725738-64-7D
                                                                                                                                     EB 725738-64-7D
                                        108-88-3 PhMe
                                                                                                                                                                STAGE(1)
                                                                                                                                                                              861
80L
80N
                                                                                               NTE
 RGT
PRO
SOL
                                                                                                                                       RCT
 RX (50)
                                                                                                                                       RX (54)
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EH 346652-91-3 SUBSTAGE(1) 1 minute, -78 deg C SUBSTAGE(2) 10 minutes, -78 deg C STAGE (2) 8 5 8

SUBSTAGE(1) room temperature SUBSTAGE(2) 10 minutes, room temperature SUBSTAGE(3) room temperature -> -78 deg C

PRO EI 583829-96-3

NTE solid-supported reactant

NEF SOLNT:
122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR
THERE ARE 122 CITED REFERENCES AVAILABLE IN THE RE
FORMAT

140:423500 CASREÄCT <u>Full-text</u>
Total synthesis of 26-fuloro-epothilone B
Koch, Guido; Loiseleur, Olivier; Altmann, Karl-Heinz
Novartis Institutes for Biomodical Research, Basel, COPYRIGHT 2007 ACS on STN 4002, Switz. Synlett (2004), (4), 693-697 CODEN: SYNLES; ISSN: 0936-5214 GGOCY Thlame Verlag Journal English L33 ANSWER 6 OF 23 CASREACT ACCESSION NUMBER: 140:4: TITLE: AUTHOR(S): CORPORATE SOURCE: PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI SOURCE:

PAGE 1-B

SN 10/563058 Page 45 of 172 STIC STN SEARCH RESULTS

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AF YIELD 86%

RCT AE 823203-10-7 RX (6)

RCT AG 1070-89-9 (Me3Si)2N.Na SOL 109-99-9 THF CON 0 deg C STAGE(2)

STAGE (3)

7. AB 823203-08-3 109-99-9 THF 1 SUBSTAGE(1) 0 deg C SUBSTAGE(2) 0 deg C -> 23 deg SUBSTAGE(3) 5 hours, 23 deg C

4

SN 10/563058 Page 46 of 172 STIC STN SEARCH RESULTS

KGT R 12125-02-9 NH4Cl SOL 7732-18-5 Water CON 23 deg C STAGE (4)

AF 823203-09-4 PRO AF NTE las REFERENCE COUNT:

last stage quench
THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS
T:
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

scavengers: A total synthesis of epothilone C Storer, R. Ian; Takemoto, Toshiyasu; Jackson, Philip S.; Brown, Dearg S.; Baxendale, Ian R.; Ley, Steven V. Department of Chemistry, University of Cambridge, EACT COPYRIGHT 2007 ACS on STN 141:140221 CASREACT Full-text Multi-step application of immobilized reagents and CASREACT L33 ANSWER 5 OF 23 ACCESSION NUMBER: TITLE: CORPORATE SOURCE: AUTHOR(S):

Chemistry--A European Journal (2004), 10(10), CB2 1EW, UK Cambridge, 2529-2547

CODEN: CEUJED; ISSN: 0947-6539 Wiley-VCH Verlag GmbH & Co. KGAA

SOURCE:

Journal English PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

A stereoselective convergent synthetic strategy was applied, incorporating polymer-supported reagents, catalysts, scavengers and catch-and-release techniques to avoid frequent aqueous work-up and chromatog, purification The enantioselective preparation of 3 key fragments theptanone I, (S)-2-methyl-6-heptenal, and thiazole II along with their elaboration via diastereoselective coupling into epothilone C is presented. The total synthesis of the cytotoxic antitumor natural product epothilone C has provided a stage for the exploitation and further development of immobilized reagent methods. 8

RX(112) OF 662 COMPOSED OF RX(50), RX(54) RX(112) N + EH ===> EI

8

SN 10/563058 Page 43 of 172 STIC STN SEARCH RESULTS PRO CA 861125-00-0

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L33 ANSWER 4 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 142:113814 CASREACT Full-teat
TITLE: Method for producing Cl-Cl5 fragments of epothilones and derivatives thereof Klar, Ulrich; Buchmann, Bernd; Schwede, Wolfgang; Schwalla, Wenner Schweing Aktlengesellschaft, Germany PCT Int. Appl., 48 pp.
DOCUMENT TYPE: Patent LANGUAGE: Patent FAMILY ACC. NUM. COUNT: 1
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:
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The invention relates to a method for preparing C1-C15 fragments I [R1a, R1b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R1aR1b = (GH2)m; m = 2 - 5; R2a, R2b = H, C1-10-alkyl, C2-10-alkyly, aryl, C7-20-aralkyl; R2aR2b = (GH2)m; n = 2 - 5; R3 = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4a, R4b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4aR4b = (GH2)p; p = 2 - 5; R3 = H, C1-10-alkyl, aryl, C7-20-aralkyl; R6, R7 = H; R6R7 = bond, O; G = X:CR8, bi- or tricyclic aryl; R8 = H, halogen, (un)substituted C1-20-alkyl, aryl, C7-20aralkyl; x = 0, (0R23)2, C2-10-alkylene-α,ω-dioxy, H(0R9), CR10R11; R23 = C1-20-alkyl; R9 = H, protecting group; R10, R11 = H, C1-10-alkyl, aryl; C7-20-aralkyl; CR10R11 = 5 - to 7-membered carbocycle; R13 = CH2OR13a, CH2-halo, RSG(:V) (GH2)3GR44R4bC(:W)R3a [V, W = O, (OR23)2, C2-10-alkylane- a, w-dloxy, H(OR9)], to form a C1-C12 fragment, RSC(:V) (GH2)3GR4R4bCR3a(0-FG14) CR2AR2b(C12)CR18DbCHR14CH2R13 [PG = H, protecting proup), which is then treated with a C13-C15 fragment, G-CR2O'GH2CHR7'R21 [R7' = H; R20' = halogon, N3, NHR29, OH, O-PG, NR29-PG, C1-20-(perfluoro)alkylaulfonyloxy, (C1-d-alkyl), deisopropylidenation/detetrahydropy ranylation with catalytic 4-MeC6H4SO3H in intermediate product I. Thus, I [Ria e Rib e R5 e Me, R2a = CH2CH:CH2-β, R2b g, R20 = OSiMe2CMe3-c, G = 2-methylbenzothiazol-5- yl, PG = SiMe2CMe3, Z = O)
 was prepared from (S)-4-(2-methyl-3-oxohept-6-en- 2-yl)-2,2-dimethyl-1,3-H, C1-6-alkyl} according to known methods. The invention also relates to the = R4b = H-a, R3 = H-B, R4a = Me-B, R6R7 = bond, R13 = CO2H, R14 = OSiMe2CMe3catalytic tetrapropylammonium perruthenate, Wittig reaction with [(3S)-3-(2-EtOH, silylation with CF3SO2SiMe2CMe3, regioselective desilylation with (1)-camphor-10- sylfonic acid, Swern oxidation with DMSO/ (∞C) 2 in CH2C12 and NO2, Cl, Br-substituted) benzyloxy, NR29SO2Me, NR29C(:0)Me, CH2C(:0)Me, R21 OH, halo, O-FG, P+Ph3Hal- (Hal = F, Cl, Br, I), P(0)(00)2 (Q = Cl-10-alkyl, Ph), P(:0)Ph2; R29 = H, Cl-6-alkyl), to form the Cl-Cl5 epothilone butyldimethyleilyl)oxylheptanal, tetrahydropyranylation, desilylation with BudNF in THF, oxidation in CH2C12 containing N-methylmorpholine N-oxide and CHO, COZRIJD, CO-halo, Rija, Ri4a = H, SOZalkyl, SOZ-aryl, SOZ-aralkyl; RijaRi4a = (CH2)o, CRI5aRi5b; o = Z - 4; Ri3b, Ri4b = H, CI-10-alkyl, aryl, C7-20-aralkyl; Ri5a, Ri5b = H, CI-10-alkyl, aryl, C7-20-aralkyl; Ri5a, Ri5a = H, CI-10-alkyl, aryl, C7-20-aralkyl; Ri5aRi5b = (CH2)q; q = 3 - 6; R20 = 0-P6, NRR29, NR3; Z = 0, H(OR12); Ri2 = H, PG of epothilones and derivs. The procedure comprises the bonding of a CI-C6 fragment, Ri3CH2CHRI4CRIARIDC(:0)CHR2aR2b, to a C7-C12 fragment, carbonyl oxidation with NaOC12 in aqueous THF/Me3COH. The produced C1-C15 epothilone intermediate products can be converted into the intrinsically active ingredients II [AK = OC(:0), OCH2, CH2C(:0), NR29C(:0), NR29SO2; dioxane via lithiation and reaction with (25,6RS)-2-methyl-6-[(tortmethylbenzothiazol-5- yl)propyl]triphenylphosphonium iodide corresponding C1-C12 fragments

RX(6) OF 60 ... AE + AB ===> AE.

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CA YIELD 318

RX(22) RCT AV 861124-76-7

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STAGE(2) RGT BI 121-44-8 Et3N

PRO BW 861124-94-9

RCT BW 861124-94-9

RX (24)

STAGE(1)

RGT BZ 26412-87-3 Pyridine-SO3 (1:1), BO 67-68-5 DWSO, BI 121-44-8 Et3N

SOL 75-09-2 CHZO12

CON 0.5 hours, 25 deg C

STAGE(2)

RGT M 12125-02-9 NH4C1

SOL 7732-18-5 Water, 60-29-7 Et2O

PRO BY 861124-97-2

RX(25) RCT S 187283-45-0, BY 861124-97-2

STAGE(1)

RGT BZ 26412-87-3 Pyridine-SO3 (1:1), BO 67-68-5 DASO, BI
121-44-8 EE3N
SOL 75-09-2 CH2C12
CON 0.5 hours, 25 deg C
STAGE(2)
RGT M 12125-02-9 NH4C1
SOL 7732-18-5 Water, 60-29-7 Et20
STAGE(2)
BGT 3 60730-34-0

STAGE(3) RGT J 69739-34-0 RGT L 108-48-5 2,6-Lutidine SOL 75-09-2 CH2C12 CON 2 hours, 0 deg C

STAGE(5) RGT GB 584-08-7 K2CO3 CON 15 minutes, 25 deg C

STAGE (4) RGT BE 7647-01-0 HCl SOL 7732-18-5 Water

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SN 10/563058 Page 39 of 172 STIC STN SEARCH RESULTS
CON SUBSTAGE(1) 5 deg C
SUBSTAGE(2) 1 minute, 5 deg C
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AF 67-68-5 DMSO, BH 79-37-8 (OCC1)2
75-09-2 CH2CL2
SUBSTAGE(1) -78 deg C
SUBSTAGE(2) 10 minutes, -78 deg C
                                                                                                                                                                                                                                                                                                                                                                                                                                                        SUBSTAGE(1) -70 deg C
SUBSTAGE(2) 10 minutes, -70 deg C
SUBSTAGE(3) 1 hour, -30 deg C
SUBSTAGE(4) -30 deg C -> -70 deg C
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             109-99-9 THE
SUBSTAGE(1) 30 minutes, -70 deg C
SUBSTAGE(2) 3.5 hours, -70 deg C
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   -70 deg C
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      SUBSTAGE(1) -70 deg C
SUBSTAGE(2) 10 minutes,
SUBSTAGE(3) 15 minutes,
                                                                                                                                                                                                                                                                                                                                                                                                                                   BL 4111-54-0 LiN(Pr-i)2
                                                                                                                                                                                                                                                                BF 279225-51-6
75-09-2 CH2C12
30 minutes, -78 deg C
                                                                                                                                                                                                                                                                                                                          RGT AG 121-44-8 Et3N
CON -78 deg C -> -10 deg
                                                                                                                                   2 hours, room temperature
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                AL 7646-85-7 ZnC12
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  BG 279226-52-7
             T 220775-18-8
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Wittig reaction
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BF 279226-51-6
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                                                                                                         104-15-4 TsOH
64-17-5 EtOH
                                      5 hours
                                                                                                                                                                                                                                                                                                                                                                                                                         STAGE (1)
STAGE(2)
RCT T
SOL 1:
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RGT 7
SOL 1
                                                                                                                                                                                                                                                        STAGE (2)
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SOL
SON
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SOL
SON
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SOL
SON
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PRO
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                                                                                     RX(16)
                                                                                                                                                          RX(17)
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SN 10/563058 Page 40 of 172 STIC STN SEARCH RESULTS RCT BJ 69739-34-0

PRO BK 924727-14-0

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 3 OF 23 CASREACT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 143:172686 CASREACT Full-text
New method for totally synthesizing natural product-epothlones Yan, Jiaqi Peop. Rep. China Faming Zhuanli Shenqing Gongkai Shuomingshu, 29 pp. ODDEN: CHXEV Patent Chinese 20021205 20021205 CN 2002-153675 CN 2002-153675 APPLICATION NO. 20030521 DATE KIND 4 FAMILY ACC. NUM. COUNT: PATENT INFORMATION: CM 1418881
PRIORITY APPIN. INFO.: PATENT NO. PATENT ASSIGNEE(S): SOURCE: DOCUMENT TYPE: INVENTOR (S): LANGUAGE:

AB The invention discloses a novel multi-step synthetic method for preparing Epothilone A and epothilone B (I; R = H or Me resp.) in a convergent approach starting from 2,2-dimethyl-3-oxopentanal, propionaldehyde SAMP hydrazone, and Et 2-methylthiazolidin-4-ylcarboxylate.

RX(97) OF 191 COMPOSED OF RX(22), RX(23), RX(24), RX(25) RX(97) AV + BS + S + J ====> CA

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33

STAGE (4)

SN 10/563058 Page 37 of 172 STIC STN SEARCH RESULTS

STAGE(2)

P 865535-39-3 V 534-17-8 Cs2003 603-32-7 Ph3As, 72287-26-4 Palladium, RGT CAT

bis(diphenylphosphino-kP)ferroceneldichloro-,

 $68-12-2~\mathrm{DMF}$ 2 hours, 0 deg C -> room temperature

T 865535-59-7 20 S PRO

T 865535-59-7 RX(11)

AQ 1310-65-2 Lion AP 865535-60-0

SOL 77 SOL 77 CON 2.1

7.32-18-5 Water, 67-63-0 Me2CHOH
2.5 hours, 60 deg C
1: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 2 OF 23 CASREACT ACCESSION NUMBER: 146:2 TITLE:

EACT COPYRIGHT 2007 ACS on STN 146:229070 CASREACT Full-text Total synthesis and antitumor activity of ZK-EPO: The first fully synthetic epothilone in clinical

development

Klar, Ulrich; Buchmann, Bernd; Schwede, Wolfgang; Skuballa, Werner; Hoffmann, Jens; Lichtner, Rosemarie

AUTHOR(S):

CORPORATE SOURCE: SOURCE:

Schering AG, Research Center Eurpos, Berlin, Germany Angewandte Chemie, International Edition (2006), 45(47), 7942-7948
CODEN: ACIEFS; ISSN: 1433-7851
Wiley-VCH Verlag GmbH & Co. KGaA
English

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

efficacy than taxanes, such as paclitaxel and second-generation epothilones, fast and efficient cellular uptake, no recognition by efflux mechanisms, and an improved therapeutic window. From about 350 active epothilone analogs synthesized by a highly convergent synthesis, ZK-EPO (I) was chosen for clin. development on the basis of its for clin, development on the basis of its This compound exhibits higher activity and outstanding preclin. data. Ŗ

SN 10/563058 Page 38 of 172 STIC STN SEARCH RESULTS

RX(84) OF 314 COMPOSED OF RX(15), RX(16), RX(17), RX(18) RX(84) BC + T + BI + BJ ===> BR

RCT BC 823203-10-7 RX(15) RGT BE 1070-89-9 (Me3Si)2N.Na SOL 109-99-9 THF

37

SN 10/563058 Page 35 of 172 STIC STN SEARCH RESULTS

100.0% DONE 3173 VERIFIED SEARCH TIME: 00.00.04

468 HIT RXNS

23 DOCS

=> d ibib abs fhit L33 1-23

COPYRIGHT 2007 ACS on STN L33 ANSWER 1 OF 23 CASREACT ACCESSION NUMBER: 146:2 TITLE:

146:251631 CASREACT Full-text
Total synthesis and biological assessment of benzimidazole-based analogs of epothilone A:

Ambivalent effects on cancer cell growth inhibition Cachoux, Frederic; Isarno, Thomas; Wartmann, Markus; Altmann, Karl-Heinz Prestwick Chemical, Illkirch, Fr. ChemBiochem (2006), 7(1), 54-57 CODEN: CBCHFK; ISSN: 1439-4227 Wiley-VCH Verlag GmbH & Co. KGaA

CORPORATE SOURCE: SOURCE:

AUTHOR(S):

Journal English

PUBLISHER: DOCUMENT TYPE: LANGUAGE: GI

The title (12R,13S)- and (12S,13S)-epoxy-benzimidazole epothilone derivs. (R12 = β -, α -H, resp.), as well as the corresponding (122)- and (12E)- Δ 12-olefin epoxide precursors, were prepared and evaluated for inhibition of growth of human cancer cell lines, such as KB-31 and KB-8511. æ

RX(30) OF 64 COMPOSED OF RX(10), RX(3), RX(4), RX(11) RX(30) AN + AC + S ====> AP

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SN 10/563058 Page 36 of 172 STIC STN SEARCH RESULTS

RCT AN 3020-28-8 RX(10)

15 minutes, room temperature RGT AO 1070-89-9 (Me3Si)2N.Ne SOL 109-99-9 THF CON 15 minutes, room temporation STAGE (1)

RCT AC 279226-82-3 CON 30 minutes, -78 deg C STAGE (2)

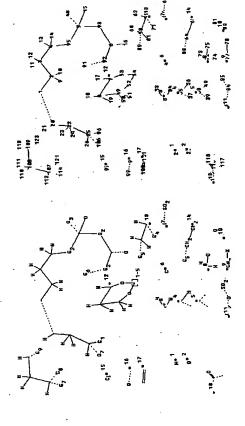
O 865535-38-2 stereoselective, Wittig reaction PRO

O 865535-38-2 Q 3144-16-9 10-C\$A P 865535-39-3 67-56-1 MeOH, 75-09-2 CH2C12 17 hours, room temperature RGT PRO SOL SOL RX (3)

S 279227-12-2 ű RX (4) STAGE(1) RGT U 280-64-8 9-BBN SGL 109-99-9 THF CON 90 minutes, room temperature

35

SN 10/563058 Page 33 of 172 STIC STN SEARCH RESULTS



25-96 25-106, 35-37 38-39 38-40 49-52 52-54; 53-54 58-89 59-71 23 24 25 26 27 28 68 71 72 73 74 75 96 97 101 106 107 108 109 110 111 112 9-50 49-51 58-59 58-60 58-61 58-89 59-62 59-71 64-65 64-88 67-68 2-3 3-4 4-95 5-93 5-48 5-15 5-95 6-92 6-16 6-93 7-8 7-53 8-83-84 84-85 91-92 98-99 107-114 107-121 109-123 115-116 116-80-81 83-84 84-85 91-92 100-101 107-108 107-112 107-114 107-8-18 8-19 20-21 20-22 22-23 22-24 22-25 25-26 25-96 25-106 2-3 2-9 2-10 3-4 3-11 3-12 4-14 4-13 4-95 5-93 5-48 5-15 5-95 18 19 21 22 2 62 64 65 67 109-113 109-123 115-116 116-117 116-118 98 99 100 17 15 60 6-16 35-37 38-39 38-40 98-99 8-49 49-52 52-54 53-54 11 12 13 14 50 51 58 59 40 93 39 95 20 35 37 38 89 91 121 123 108-110 10 48 chain nodes 115 22-25 67-68 2-74 hain bonds

SN 10/563058 Page 34 of 172 STIC STN SEARCH RESULTS

7-17 8-18 8-19 20-21 22-23 22-24 25-26 58-59 58-60 58-61 59-62 64-65 72-73 72-74 07-108 107-112 108-109 108-110 108-111 109-113 2-9 2-10 3-11 3-12 4-14 4-13 32-33 32-34 35-36 49-50 49-51 77-78 100-101 exact bonds :

61:[*1],[*2]

62:[+3];[+4],[+5]

G3:H,[*6]

G4:X,OH,O,[*7]

G5:[*8],[*9],[*10],[*11]

G6: (*12], [*13], [*14]

G7: [*15], [*16], [*17]

G8:0, N, X, [*18]

39:0, P, X

23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 40:CLASS 65; CLASS 67; CLASS 68; CLASS 71; CLASS 72; CLASS 95:CLASS 96:CLASS 97:Atom 98:CLASS 99:CLASS 100:CLASS 109:CLASS 110:CLASS 111:CLASS 112:CLASS 113:CLASS 52:Atom 53:Atom 54:Atom 58:CLASS 59:CLASS 6:CLASS 7:CLASS 8:CLASS ASS 15:CLASS 16:CLASS 1 36:CLASS 37:CLASS 38:CLASS 39:CLASS 85:CLASS 81:CLASS 83:CLASS 84:CLASS 118; CLASS 121; CLASS 123; CLASS # 22:CLASS 35:CLASS 80:CLASS 51:CLASS

aturation

: Unsaturated : Polycyclic ype of Ring System

fragments assigned product role:

fragments assigned reactant/reagent role:

code mappings:

468 REACTIONS) 23 SEA FILE=CASREACT SUB=L30 SSS FUL L31 (

133

33

31

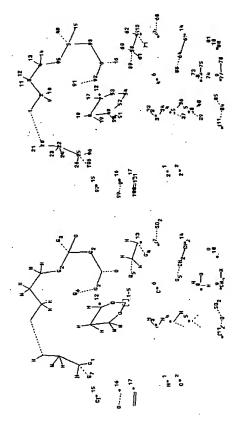
2-9 2-10 3-11 3-12 4-14 4-13 7-17 8-18 8-19 20-21 22-23 22-24 25-26 32-33 32-34 35-36 49-50 49-51 58-59 58-60 58-61 59-62 64-65 72-73 72-74

83-84 84-85 91-92 98-99

0-22

SN 10/563058 Page 31 of 172 STIC STN SEARCH RESULTS

Structure attributes must be viewed using STN Express query preparation: Uploading Lib.str



22-25 25-96 25-106 35-37 38-39 38-40 49-52 52-54 53-54 58-89 59-71 19-50 49-51 58-59 58-60 58-61 58-89 59-62 59-71 64-65 64-88 67-68 7-17 8-18 8-19 20-21 20-22 22-23 22-24 22-25 25-26 25-96 25-106 2-3 2-9 2-10 3-4 3-11 3-12 4-14 4-13 4-95 5-93 5-48 5-15 5-95 1-20 2-3 3-4 4-95 5-93 5-48 5-15 5-95 6-92 6-16 6-93 7-8 7-53 22 23 24 25 26 67 68 71 72 73 13 14 15 17 18 19 21 ; 58 59 60 61 62 64 65 35 37 38 39 40 45 98 99 100 80-81 83-84 84-85 91-92 100-101 35-37 38-39 38-40 98-99 8-49 49-52 52-54 53-54 10 11 12 48 50 51 83 xact/norm bonds ing/chain bonds in node

SN 10/563058 Page 32 of 172 STIC STN SEARCH RESULTS

77-78 100-101

G2:(*3),[*4],[*5]

G1:{*1], [*2}

G3:H,[+6]

G4:X,OH,O,[+7]

G5:[*8],[*9],[*10],[*11]

G6: [*12], [*13], [*14]

67:[*15],[*16],[*17]

CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLAS: 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 67:CLASS 68:CLASS 71:CLASS 72:CLASS 73:CLASS 22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 40:CLASS BB:CLASS 95:CLASS 96:CLASS 97:Atom 98:CLASS 99:CLASS 100:CLASS 51:CLASS 52:Atom 53:Atom 54:Atom 58:CLASS 59:CLASS 36:CLASS 37:CLASS 38:CLASS 39:CLASS 83:CLASS 84:CLASS 85:CLASS 80:CLASS 81:CLASS 35:CLASS 65:CLASS 78:CLASS 91:CLASS Match level 101:CLASS

Generic attributes :

: Unsaturated : Polycyclic Saturation Type of Ring System

560 SEA FILE=REGISTRY SSS FUL L1 69 SEA FILE=CASREACT ABB=ON PLU=ON L3 STR

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation: Uploading L31b.str

SN 10/563058 Page 29 of 172 STIC STN SEARCH RESULTS

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			E	DE 1997-19735575	K	1997080
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			ş	WO 1998-EP5064	3	1998081
OTHER SOURCE(S):	CASREACT	130:168162	7 .:	CASREACT 130:168162; MARPAT 130:168162		
15						

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2

R6 = H), useful for the preparation of epothilone and epothilone deriva, are prepared from (R)-, (S)- or (1)-pantolactone (II; R8 = H) via the prepared from (R)-, (S)- or (1)-pantolactone (II; R8 = H) via the prepared with 3,4-dipydropyrana and pyridinium p-toluenesulfonate and reduction of THP ether II (R8 = THP) with DIBAL-H, Wittig reaction of lactol III with MePh3P+Br-/BuLi, oxidation of pentenol IV (R9 = CH:CH2, R10 = CH:CH2, R10 = CH:CH2, R10 = CH:CH2, R10 = CH(OH)CH2R5) with N-methylmorpholine N-oxide/FPAP and oxidation of keto aldehyde IV (R9 = CH:CH2, R10 = CH(OH)CH2R5) with N-methylmorpholine N-oxide/FPAP and oxidation of keto aldehyde IV (R9 = CH2CH0, R10 = CH:CH2, R10 = CH(OH)CH2R5) or hewenol IV (R9 = CH2CAP, R10 = CH:CH2, R10 = CHCH2R5) can be oxidized then alkylated with LiN(CHMe2)2 and R6Z (Z = leaving group) and the resulting ketone IV (R9 = CH:CH2, R10 = CCHRSR6); can hydroborated and Compds. I (R1 = H, OH, OR7; R2 = H, protective group; R3, R4 = H, C1-10-alkyl, C7-10-aralkyl; R3R4 = (GH2)m; R5, R6 = H, C1-10-alkyl, aryl, C7-20-aralkyl; R7 = C1-20-alkyl, C7-20-aralkyl; R1 ≠ OH, when R2 = SiMe2CMe3, R3 = R4 = R5 = Me, oxidized as above, leading to

SN 10/563058 Page 30 of 172 STIC STN SEARCH RESULTS

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http://www.cas.org/support/stngen/stndoc/properties.html

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FILE CONTENT:1840 - 6 Oct 2007 VOL 147 ISS 16

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this file contains CAS Registry Numbers for easy and accurate substance identification.

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT

27

SN 10/563058 Page 27 of 172 STIC STN SEARCH RESULTS

protecting group; R11 = H, protecting group] including all the stereoisomers and their mixts. are prepared E.g., title compound (S)-III [R5 = R6 = Me, R9 = R11 = H, R10 = TBD52] was prepared in 6 steps from D-(-)-pantolactone via neaction with 3,4-dihydro-2H-pyran, hydride reduction, Wittig reaction with methyltriphenylphosphonium broamles, protection of OH with TBDPS-C1, detertrahydropyranyl, and reduction with borane-THF.

L102 ANSWER 23 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:116658 CAPLUS Full-text
DOCUMENT NUMBER: 130:16616 CAPLUS Full-text
DOCUMENT NUMBER: 130:16616 CAPLUS Full-text
Now (C13-C15)-fragments, method for their preparation and their application for synthesis of epothllone and epothllone derivatives
ALA, ULitah; Schwarty Schward; Schwalla, Remaer; Buchmann, Bernd; Schirner, Michael Schirner, Michael Schirner, Michael Schirner, Michael Schirner, Ger. Offen., 14 pp.

DOCUMENT TYPE: Gernan
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

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	·	A1	1999	19990218	Ī	5 5	-866	1998-2299608	608		-	19980810	910
	Ī	A2	1999	19990218	_	WO 15	-866	1998-EP5064	64		-	19980810	310
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	_	7	2003	20030731	_	JS 20	-000	2000-485292	92		Ñ	20000503	903
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						WO 15	1-86	1998-EP5064	54	-	-	9980810	310
	U	CASREACT 130:168163; MARPAT 130:168163	CI 13	0:16	3163	M.	PAT	130	168	63			

SN 10/563058 Page 28 of 172 STIC STN SEARCH RESULTS

AB The title compds. [I; II; Rl = H, alkyl, aryl, aralkyl; RZ = H, protecting group; R3 = OH, halo, ORG; RG = protecting group; R4 = H, alkyl; R5 = H, alkyl, aryl, aryl, aryl, aralkyl] are prepared E.g., title compound I [Rl = Me, R2 = TBDPS, R3 = TBDMS] was prepared in 6 steps from L(-)-imalic acid via reduction, 3-O-protection of 3(S)-hydroxy-2-tetrahydrofuranone, hydride reduction, into opening and chain longthening, 1-O-protection of 3(S)-(tert-butyldiphenylsilyloxy)-1, 4-pentanoglol, and oxidation of 3(S)-(tert-butyldiphenylsilyloxy)-5-(tert-butyldimethylsilyloxy)-2- pentanol. This was further treated with Et (2-methyl-4- thiazolylmethyl)phosphonato in THF-hexano containing Buli to give [E,3S)-I([dimethyl(1,1-dimethyl)silyloxy)-3-[([1,1-dimethylethyl)silyloxy)-4-(2-methylthiazol-4-ene.
yl)pent-4-ene.

L102 ANSWER 24 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:116657 CAPLUS FULL-text
DOCUMENT NUMBER: 130:163162

TITLE: New method for the preparation of the (C1)-C(6)-segment of epothilors and epothilors and epothilors.

INVENTOR(S): Klar, Ulrich; Schwede, Wolfgang; Struck, Michael and Schringry Michael M

PATENT NO. KIND DATE APPLICATION, NO. DE 19735574 A1 19990211 DE 1997-19735574 CA 2299608 A2 19990218 CA 1998-2299608 WO 9907692 A3 19990218 WO 1998-EP5064 WO 9907692 A3 19990219 W. AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, E, E, S, FI, GB, GB, GH, GH, WI, ID, IL, IS, JP, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MN, PL, PT, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, US, UZ, VNY, ZW W. GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, FI, FR, GB, GR, LE, TV, LU, NC, NL, PT, SE, BF, BJ, CM, GA, GM, AM, MI, NE, SM, TD, TG AU 9893409 BE 1005465 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, LL, DA, CONTSTS, TR, TR, CA, CA, CH, CA, CA, CA, CA, CA, CA, CA, CA, CA, CA	Δ	-	19980810	19980810		G, Q	JP, KE,	C, MN, MW, MX,	TM, TR,		GH, QY,	I, BF, BJ, CF,		19980810	19980810		, LU, NL, SE, MC, PT,		01908091
HIND DATE	LICATIÓ	1997-197	1998-229			BY,	ΙΓ,	Ř,	SI,		/, AT, BE	, PT, SE	o, TG	1998-934	1998-946		(, IT, L		2000-506
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SN 10/563058 Page 25 of 172 STIC STIN SEARCH RESULTS

A 19980320 W 19980810 DE 1998-19813821 WO 1998-EP5064

MARPAT 130:196529 OTHER SOURCE(S): GI

new compds, interact with tubulin by stabilizing formed microtubuli. They are capable of influencing cell division in a phase-specific manner and are suitable for the treatment of malignant tumors, and as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant melanoma, and cutte lymphocytic and myelocytic leukemia. They are also suited for anti-angiogenesis therapy and for the treatment of chronic inflammatory diseases (posisis, arthritis). To prevent uncontrolled cell growth on, and invention can be used alone or, to achieve additive or symergistic effects, in combination with other principles and substance categories used in tumor etc.; Y = 0, H2, Z = 0, (H, OH), (H, protected OH); Rla, Rlb = H, alkyl, aryl, aralkyl, or together = (CH2)m where m = 2, 3, 4, 5; R2a, R2b = H, alkyl, aryl, aralkyl, or together = (CH2)n where n = 2, 3, 4, 5; when D-E = CH2CH2 or when P-E = CH2CH2, aryl, aralkyl, aryl, aralkyl, Ra, RAb = H, alkyl, aryl, aralkyl, or together = (CH2)p where p = 2, 3; 4, 5; D-E = CH2CH2, CH3, CH3, CH4CH2, R5 = H, alkyl, aryl, aralkyl, R6, R7 = H, cogether = a saturated bond or 0; R8 = H, alkyl, aryl, aralkyl, all of which may be substituted are prepared. Thus, the title tetramethylcyclohexadec-13-en-2,6-dione (II) were prepared in many steps. The ,16S(E))-4,8-dihydroxydiseases (psoriasis, arthritis). To prevent uncontrolled cell growth on, an for better tolerability of, medical implants, the derivs. can be introduced (1-methyl-2-(2-methyl-4-thiazolyl)ethenyl)-1-oxa-5,5,9,13-The compds. provided (4S,7R,8S,9S,13E,16S(E))- and (4S,7R,8S,9S,13Z into or applied to polymeric materials. ethyl-16therapy. 2

L102 ANSWER 22 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN 1999:116659 CAPLUS Full-text DOCUMENT NUMBER: 130:168164 130:168164 Firstmethod f TITLE: New (C1-C6)-fragments, method f

New (C1-C6)-fragments, method for their preparation and their application for synthesis of epothilone and

epothilone derivatives

Skuballa, Werner; Buchmann, Bernd; Klar, Ulrich; Schwede, Wolfgang;

INVENTOR(S):

Schirner, Michael Schering A.-G., Germany Ger. Offen., 18 pp.

PATENT ASSIGNEE(S): SOURCE:

SN 10/563058 Page 26 of 172 STIC STN SEARCH RESULTS

CODEN: GWXXBX Patent German DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

PA !	PATENT NO.			KIND		DATE	ļ	.~ •	APPLICATION NO	2	NO NO	9		ä¦	DATE	ļ
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III

The title compds. [I; II; III; R1, R2 = H, alkyl, aryl, aralkyl; R3 = CH2OH, CH2OR; R4 = OH, OR; R = CR7R8; R7, R8 = H, alkyl, aryl, or R7R8 = (CH2)n; n = 2-6; R5, R6 = H, alkyl, aralkyl, or R5R6 = (CH2)n; m = 2-5; R9, R10 = H, 2

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from which structure-activity- relationships can be deduced. Epothilone A (R=H) Epothilone B (R=Me) Epothilone C (R=H) Epothilone U (R=Me).

DATE The preparation process, intermediate products pharmaceutical use of epothilone derivatives Buchmann, Barnd; Klar, Ulrich; Skuballa, Warnar; Schwede, Wolfgang; Michael; Menrad, Andreas APPLICATION NO. 2000:15195 CAPLUS Full-text Schering A.-G., Germany PCT Int. Appl., 86 pp. CODEN: PIXXD2 132:64110 Schirner, German Patent CAPLUS : TNDOO L102 ANSWER 20 OF 24 ACCESSION NUMBER: PATENT ASSIGNEE(S): SOURCE: FAMILY ACC. NUM. CO PATENT INFORMATION: DOCUMENT NUMBER: PATENT NO. DOCUMENT TYPE: LANGUAGE: INVENTOR(S): TITLE:

CU, CZ, IS, JP, MK, MN, TJ, TM, KZ, MD, 19980630 19990513 19990630 DE, DK, CF, CG, 19980630 19990513 19990630 9990630 **£** 3 8 K B L G я, ВЕ, , UG, ZW, AT, BE, C MC, ML, PT, SE, E DE 1999-19930060 DE 1999-19923001 AU 1999-19830060 DE 1999-19923001 AT, BE, PT, SE, CASREACT 132:64110; MARPAT 132:64110 SI, 15, WO 1999-EP4915 1999-EP4915 ¥,8,E ᄶ SE, ZW, 86, 15, 28, 28, 8,4,4,5,5 3,4,4,5,5 SZ, 20000210 20001116 20000117 ¥ 8 ጟ 8 ¥ St, 88, 20000106 AZ, GD, LC, PT, UZ, SD, IE, ¥.8.€ PL, US, 3.6.7 AT, FI, KR, ď, . 388 SA, TE ES, PRIORITY APPLN. INFO.: 주 중 중 중 주 £58£8 WO 2000000485 DE 19830060 DE 19923001 AU 9950369 DK, TR, TR, GH, CI, OTHER SOURCE(S): GI RW:

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C1-10-hydroxyalkyl, C1-10-haloalkyl; X = 0, (0R9)2, C2-10-alkylene=a, w-dioxy, CRINR12; CX = G(ORNO); R9 = G1-20-alkyl, R10 = H, protesting group; R11. R12 = H, C1-10-alkyl, aryl, C7-10-aralkyl; R11R12 = GH2, C5-7-carbocyclic ring; Y = 0, CY = CH2; CZ = GH(OR13), R13 = H, protecting group] which are prepared via cyclization of ketones II [R15 = H, M halogen; OR15, coSCRAIS; R15a = H, C2-alkyl, SO2-aralkyl; GH2)o, CRIGARIGb; R15b = H, C1-20-alkyl, aryl, C7-20-aralkyl; R10a, R10a, R10b = H, G1-10-alkyl, aryl, C7-20-aralkyl; aryl, C7-10-aralkyl; RlaRlb = (CH2)m, m = 2 - 5; R2a, R2b = H, C1-10-alkyl, aryl, C7-10-aralkyl; R2aR2b = (CH2)n, n = 2 + 5; R3 = H, C1-10-alkyl, aryl, C7-10-aralkyl; R4b = H, C1-10-alkyl, aryl, C7-10-aralkyl; R4aR4b = CH2Dn, m = 2 - 5; D-E = CH2CH2, CH2CH, CT4Dbond, C, oxizane ring, CH2)m, m = 2 - 5; D-E = CH2CH2, CH2CH, CT4Dbond, C, oxizane ring, CH(OH)CH(OH)CH(OH)CH(OH)CH2; R5 = C1-10-alkyl, aryl, C7-10-aralkyl; R6, R7 = H, R6R7 = 0, bond; R8 = C1-10-alkyl, C7-10-aralkyl; R25 = H, C1-10-alkyl, B

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R16aR16b = (CH2)q; o = 2 - 4; q = 3 - 6). Thus, epothilone derivative III was prepared via macrolactonization of carboxylic acid IV with 2,4,6-trichlorobenzoyl chloride and Et3N in THF followed by deprotection with aqueous CF3002H in CH2C12. I cooperate with tubulin by stabilizing formed microtubuli.

THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT COPYRIGHT 2007 ACS on STN CAPLUS L102 ANSWER 21 OF 24

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call division phase-specifically and are suitable for treating malignant tumors such as cancers of the ovaries, stomach, colon, glands, breasts, lungs, thead and neck, malignant malanoma and acute lymphocytic and myelocytic leukemia. These compds, are also suitable for anti-angiogenesis therapy and for treating chronic inflammatory diseases (psoriasis, arthritis) and can be deposited on or in polymer materials in order to prevent uncontrolled cell proliferations on medical implants and to improve the compatibility. These derivs. can be used alone or in combination with other principles and classes of substances that can be used in the therapy of tumors to achieve additive or They are able to influence the stabilizing the microtubuli which are formed. synergistic effects.

Preparation of epothilone derivatives useful as Klar, Ulrich; Skuballa, Warnar; Buchmann, Bernd; Schwede, Wolfgang; 1UUS COPYRIGHT 2007 ACS on STN 2000:573798 CAPLUS Full-text Schering A.-G., Germany PCT Int. Appl., 141 pp. Schirner, Michael pharmaceuticals CODEN: PIXXD2 133:177064 Patent German CAPLUS LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: L102 ANSWER 18 OF 24 ACCESSION NUMBER: DOCUMENT NUMBER: PATENT ASSIGNEE(S): DOCUMENT TYPE: INVENTOR(S): SOURCE: TITE

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US 2001-913163 MARPAT 133:177064

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OTHER SOURCE(S): GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

prepared Thus II was prepared in a multistep sequence from the starting materials III and IV. The novel compds. interact with tubulal by stabilizing the formed microtubuli. The compds. are able to influence the call division in a phase-specific manner and are suited for treating malignant tumors, for RID = Me; R2 = Me, Et, Pr; X = 2-pyridyi, 2-methyl-4-thiazolyl or 2-methyl-4-owazoly; and the N and/or S atoms in X can be in a oxidized form; and if R2 and R8 = Me, X can only be a 2-pyridyl residue which is optionally oxidized at the nitrogen atom) and all possible stereoisomers and their mixts were conjunction with addnl. constituents and substance classes which can be use in Novel epothilone derivs. I (R4 = R5 = H, C1-C10 alkyl, aryl, C7-C20 aralkyl; R6, R7 are each H, or together an addnl. bond or O; R8 = Me or H; R1a, R1b together = trimethylene; R2 = Ph. CH2Ph; X = 2-pyridyl, 2-methyl-4-thiazolyl, 2-methyl-4-oxazolyl, or R1a, R1b together = trimethylene; R2 = Me, Et, Pr; X 2-pyridyl, 2-methyl-4-thiazolyl, 2-methyl-2-methyl-4-oxazolyl, 2-methyl-3-methyl-4-thiazolyl, 2-methyl-4-oxazolyl; or simultaneously R1a = example, ovarian cancer, gastric carcinoma, colon cancer, breast cancer, lung cancer, had and neck cancer, maldjanat metakoma, and acute lymphocytic and myelocytic leukemia. The inventive compas, are suited for use in anti-angiogenic therepy as well as for treating chronic inflammatory diseases (psoriasis, arthritis). In order to prevent uncontrolled cell proliferations and to improve the compatibility of medical implaints, the inventive compds. can be applied or incorporated in polymeric materials. The inventive compds. can be used alone or in order to achieve additive or synergistic effects, in Ħ

Klar, Ulrich; Skuballa, Kerner; Schwede, Wolfgang; Buchmann, Bernd COPYRIGHT 2007 ACS on STN: 332415 CAPLUS Full-text 2000:332415 CAPLUS Epothilones. CAPLUS L102 ANSWER 19 OF 24 ACCESSION NUMBER: AUTHOR(S):

Preclinical Drug Research, Schering AG, Germany, CORPORATE SOURCE: SOURCE:

Berlin, D-13342, Germany Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March 26-30, 2000 (2000), ORGN-288. American Chemical Society: Washington, D. C. CODEN: 69CLAC

Conference; Meeting Abstract English DOCUMENT TYPE: LANGUAGE: AB The I

behavior of paclitaxel regarding its action on the tubulin system although the chemical structures are quite different. Despite its impressive antiproliferative effects also against multi drug resistant cell lines epothilone which allows an efficient preparation of large ants. of strategic important building blocks with high optical purity, high flexibility regarding structural modifications in most parts of the mol., efficient syntheses of analogs yielding sufficient amts. for in vivo characterization. Using this methodol., more than 250 analogs of epothilone B and D have been synthesized for epothilone analogs with improved properties is obvious. In contrast to paclitaxel structural modifications can be achieved more easily by total synthesis. Therefore we have developed a highly convergent total synthesis The new natural product class of epothilones seems to parallel the biol

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

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Epothilone derivs. I (Rla, Rlb = H, Cl-Cl0-alkyl, aryl, C7-C20-aralkyl; (GH2) m = 1-5; GGCGGT2, Raz, R2b = H, Cl-Cl0-akyl, aryl, G7-C20-aralkyl; (GH2) n = 2-5; E = A or B where t = 1-2; G, Gl = H, halogan, CN, R24, Cl-C20-acyl, C1-C20-acyloxy, OR24, OO2R24, N3, N02, NR24aR24b; R24a, R24b = R24, CGCD-acyloxy, OR24, OO2R24, N3, N02, NR24aR24b; R24a, R24b = R24, GGCD-acyloxy, R3 = H, G1-Cl0-alkyl, aryl, G7-C20-aralkyl, R14 = H, OR14a, halogen; R3b = OPG14, R3b, R4 = bond; R4a, R4b = H, F, G1-Cl0-alkyl, aryl, G7-C20-aralkyl, G7-C20-aralkyl,

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Preparation of new epothilone derivatives and their
                                                                                                                                Skuballa, Werner; Buchmann, Bernd;
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PCT Int. Appl., 54 pp.
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SN 10/563058 Page 20 of 172 STIC STN SEARCH RESULTS

LANGUAGE: German FAMILY ACC. NUM. COUNT: 1 PATENT INFORMATION:

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Epothilone deriva. I (Rla, Rlb = H, Cl-Cl0 alkyl, aryl; C7-C20 aralkyl; or together are (GH2)m m = 1-5; or CH2OGH3; R2a, R2b = H, Cl-Cl10 alkyl, aryl; C7-C20 aralkyl; or together are (GH2)n n = 2-5; Gl-G-E-E1 = CR3aR3b-CR4-CH-C12; CR3aR3b-CR4-CH-CH2; CR3aR3b-CR(T)R4-CHC(T)-CH2; (C.3.*epoxy)-CR3aR3b-CR4OGH-CH2; CR3aR3b-CR4-CH=CH where R3a = H, Cl-Cl0 alkyl, aryl; C7-C20 aralkyl; R14 = H, OR14a, halogan, OSOZR4b; R3b = OPG14 OFF:R3b, R14a = bond; R4 = H, C1-Cl0 alkyl, aryl; C7-C20 aralkyl; R5 = H, Cl-Cl0 alkyl, aryl; C7-C20 aralkyl; R6, R7 = H, O, bond; R8 = H, C1-Cl0 alkyl, aryl; C7-C20 aralkyl; R6, R7 = H, O, bond; R8 = H, C1-Cl0 alkyl, aryl; C7-C20 aralkyl; R6, R7 = H, O, bond; R8 = H, C1-Cl0 alkyl, aryl; C7-C20 aralkyl; X = O, OR23, C2-Cl0-alkylane-c, ab alkyl which can be a straight chain or branched; H/OR9 or the group CR10R1 where R23 = C1-C20 aralkyl or R10, R11 together form a 5-7 membered carbocyclic ring; Y = O or 2 H atoms; Z = O or H/OR12 where R12 = H or a protecting group) were prepared in addition to all possible stereoisomers and mixts. Thus II was prepared from (1)-1-acetoxypantan-4 one in a multistep synthesis. These epothilone derivs. interact with tubulin by

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AB 16-Halogen epothilone derivs. I (RIa, RIb = RZa, RZb = H, CI-CIO-alkyl, aryl, C7-C2O-aralkyl, (CH2)m m = 2-5; R3 = H, CI-CIO-alkyl, aryl, C7-C2O-aralkyl, (CH2)p p = 2-5; D = 0, CH2, R4a, R4b = H, CI-CIO-alkyl, aryl, C7-C2O-aralkyl, (CH2)p p = 2-5; D = 1,2-ethanediyl, 1,2-ethanediyl, aryl, C7-C2O-aralkyl, (CH2)p p = 2-5; D ethanediyl, 1(2)-hydroxy-1,2-ethanediyl, CH2OH; R5 = H, CI-CIO-alkyl, aryl, C7-C2O-aralkyl, CO2+1kyl, CH2OH; R6, R7 = H, Dond, O. RADHZ, C7-C2O-aralkyl, CA2-alkyl, CH2OH; R6, R7 = H, Dond, O. RADHZ, C7-C2O-aralkyl, CA2-alkyl, CH2OH; R6, R7 = H, Dond, O. R8 = halogen, CN; X = 0, two alkoxy groups OR23, C2-C1O-alkylane-a, a-dihydroxy group straight or branched chain, H/OR9, CH1OR11 where R23 = C1-C2O-alkyl; R9 = H, or protecting group; R10, R11 = H, C1-C1O-alkyl, aryl, C7-C2O-aralkyl; F9 = H, or protecting group; R10, R11 = H, C1-C1O-alkyl, aryl, C7-C2O-aralkyl; F7 membered carboxyclic ring; T-Y = OC(-O), OCH2, CH2C(-O), NR24SO2; R24 = H, C1-C1O-alkyl; Z = O, H/OR12 where R12 = H or protecting group) were prepared in addition to all possible stereoisomers and mixts. Thus II was prepared from z-methyl-4-thiazolecarboxaldehyde in a multistep synthesis. The ICSO of II was 5.1 nM on MCF-7 breast tumor and had an ICSO of 37 nM on the multidrug resistant carchnoma NCI/ADR.

L102 ANSWER 16 OF 24 CAPIJUS COPYRIGHT 2007 ACS on STN	SAPLUS	COPYRIGHT 200	07 ACS on STN ,	
ACCESSION NUMBER:	2000	2000:592720 CAPLUS Full-text	JS Full-text	
DOCUMENT NUMBER:	133:	133:193027		
TITLE:	Prep	ration of new	Preparation of new epothilone derivatives having	ves having
	phari	naceutical app	pharmaceutical application as antitumor agents	r agents
INVENTOR(S):	S	, Ulrich; Sch	Klar, Ulrich; Schwede, Wolfgang;	
	Buch	nann, Bernd; S	Buchmann, Bernd; Skuballa, Werner;	
	Schi	mer, Michael;	Schirner, Michael; Grimm, Michael	
PATENT ASSIGNEE(S):	Sche	ring Aktienges	Schering Aktiengesellschaft, Germany	
SOURCE:	PG.	PCT Int. Appl., 70 pp.	dd C	
	80 80 80 80 80 80 80 80 80 80 80 80 80 8	CODEN: PIXXD2		
DOCUMENT TYPE:	Patent	ř.		
LANGUAGE:	German	5		
FAMILY ACC. NUM. COUNT:				
PATENT INFORMATION:				
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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SN 10/563058 Page 15 of 172 STIC STN SEARCH RESULTS

	20011019	20011026	20011029	20011030	20011129	20020606	20041018	20050802	20050831	20070411	A 19990430	A 19991104	A 20000309	A 20000327	A3 20000501	W 20000501	A3 20011019	A3 20020606
	2001-MN1305	2001-106053		2001-PA11039	2001-9859		2004-965802	2005-MN837	2005-214988	2007-104224	1999-19921086	1999-19954228	2000-10013363	2000-10015836	2000-615619	2000-IB657	2001-MN1305	2002-979939
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•	IN 2001/M01305	BG 106053	NO 2001005278	MX 2001PA11039	. ZA 2001009859	US 7125893	US 2005113429	IN 2005/M00837	US 2006046997	JP 2007224038	PRIORITY APPLN. INFO.:				•		•	

up the mols. Thus, [45,7R,85,95,132,165(E)]-4,8-dihydroxy-16-[1-methyl-2-(2-pyi4dy) ethemyl]-1-oxe-5,5,9,13-tetramethyl-7-(3-buthyl)-13-cyclohoxadecene-2,6-dione was prepared in several steps starting from (45)-4-(2-methyl-1-oxe-2-propyl)-2,2-dimethyl[1,3]dioxane and 5-(trimethylsily)-4-pentynylmagnesium The title compds. were prepared by various combinations of 3 fragments making MARPAT 133:321769 OTHER SOURCE(S):

Preparation of new epothilone derivatives and their 19990218 DE 1999-19908767 : DE 1999-19908767 Skuballa, Werner; Buchmann, Bernd; APPLICATION NO. pharmaceutical uses Klar, Ulrich; Schwede, Wolfgang; 2000:738730 . CAPLUS Full-text COPYRIGHT 2007 ACS on STN Schirner, Michael Schering A.-G., Germany Ger. Offen., 74 pp. CODEN: GMXXBX MARPAT 133:309795 20001019 KIND DATE 133:309795 Patent German CAPLUS A1 SUNT: DE 19908767 PRIORITY APPLN. INFO.: OTHER SOURCE(S): LI02 ANSWER 14 OF 24 ACCESSION NUMBER: PATENT ASSIGNEE(S): FAMILY ACC. NUM. CON PATENT INFORMATION: DOCUMENT NUMBER: PATENT NO. DOCUMENT TYPE: INVENTOR(S): LANGUAGE: SOURCE: TITLE: IJ

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alkylene-a, w-dloxy group straight or branched, OR9 or the CRIORII group where R23 = alkyl, R8 = H or protecting group and R10,R11 = same or different H, alkyl, aryl, aralkyl or R10,R11 = together with methylene are a 5-7 membered carbocyclic ring; Y = 0 or two H; Z = 0 or H/OR12 and R12 = H or a protecting group) were prepared Thus E- and Z-II were prepared via a multistep synthesis. I cooperate with tubulin by stabilizing formed microtubuli. I are able phase specifically to affect the cell division and are suitable for the treatment of malignant ovarian, stomach, colon, acieno, breast, lung, head and can be used alone or to achieve additive or synergistic effects in combination with further principles and substance classes applicable in tumor therapy. aeryl, aralkyl or (GH2)m,n m, n = 2-5; R3 = H, alkyl, aryl, aralkyl; R4a,R4b = same or different H, alkyl, aryl, aralkyl or (GH2)p = 2-5, GH2CH2, CH-CH, C-tplbond.C, epoxy, GH(6H)GH(H), GH(GH)GH2; D-E = a group; R5 = H, alkyl, aryl, aralkyl; R6,R7 = H, bond, 0; R8 = H, alkyl, aryl, aralkyl; X = 0, OR23 uncontrolled cell proliferations and to improve the compatibility of neck tumors, malignant melanomas, acute lymphocytic and myelocytic leukemia. Derivs. of I are suitable for use in anti-angiogenic therapy as well as for treating chronic inflammatory diseases (psoriasis, arthritis). In order to medical implants I can be applied or incorporated into polymeric materials. New epothilone derivs. I (Rla, Rlb - R2a, R2b - same or different prevent 8

Preparation of 16-halogen epothilone derivatives and Schering Aktiengesellschaft, Germany PCT Int. Appl., 105 pp. Buchmann, Bernd; Schwede, Wolfgang; 1US COPYRIGHT 2007 ACS on STN 2000:592721 CAPLUS FUll-text their use as antitumor agents, Klar, Ulrich; Skuballa, Warner; Schirner, Michael CODEN: PIXXD2 133:193028 L102 ANSWER 15 OF 24 PATENT ASSIGNEE(S): ACCESSION NUMBER: DOCUMENT NUMBER: INVENTOR (S): SOURCE: TITLE:

CAPLUS

German Patent SOUNT: FAMILY ACC. NUM. OC PATENT INFORMATION: DOCUMENT TYPE:

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SN 10/563058 Page 13 of 172 STIC STN SEARCH RESULTS

FAMILY ACC. NUM. COUNT: 3 PATENT INFORMATION:

PATENT NO.		KIND	_	DATE		Α,	APPLICATION NO.	CATI	z Z		!	Õ	DATE	-		
WO 2000066589	¦ _	F		20001109	1109		WO 2000-IB657	0	B657			1 %	20000501	6		
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CA 2371226		A1		20001109	1109	Ü	S 50	2000-2371226	3712	56		2	20000501	5		
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EP 1173441		A1		20020123	1123	ΙΉ	EP 20	2000-922826	2282	9		20	20000501	0		
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JP 2002543203		E		20021217	1217		JP 20	2000-615619	1561	o.		. 50	20000501	5		
EE 200100568		K	٠.	20030217	1217	ш	E 20	2001-568	89			2	20000501	5		
NZ 514989		4		2004022	7227	2	NZ 20	2000-514989	1498	6		2	20000501	5		
AU 772750		B2	٠	20040506	9050	۹,	AU 20	2000-43103	3103		~-	20	20000501	5		
IN 2001MN01305	S	4		20070504	504	-	IN 20	2001-MN1305	N130	'n		2	20011019	119		
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NO 2001005278		K	-	20011221	1221	Ζ,	NO 20	2001-5278	278			50	20011029	53		
MX 2001PA11039	6	Κ		20030630	9830	2,	MX 20	2001-PA11039	A110	39	-	8	20011030	8		
US 7125893		B1		20061024	1024	9	US 20	2002-979939	7993	, O		20	20020606	90		
IN 2005MN00837	7	4		20070608	8090		IN 20	2005-MNB37	N837			8	20020802	05		
US 2006046997		Al		20060302	305	5	US 20	2005-214988	1498	&	,	ຂ	20050831	31		
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							US 20	2002–979939	7993	0	Κ	A3 20	20020606	90		
OTHER SOURCE(S):		MARF	ĀŢ	133:3	MARPAT 133:362656	9										

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

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replace a with b) = H, substituted alkyl, aryl, aralkyly.(GH2)ra-C.tpibond.(or =)C-(GH2)pa-R26a, Q, Ql where n = 0-5; ra, rb = the same or different and = 0-4; ps. rb = the same or different and = 0-3; R3a = H, substituted alkyl, aryl or aralkyl, R3b = GH, OFG14; R14 = H, OR14a, halogen and R14a = H, SO2-alkyl, SO2-aryl or SO2-aralkyl; R4 = H, substituted alkyl, aryl or aralkyl, halogen, OR25, CN; R26a, R26a, R26a = same or different = H, substituted alkyl, aryl or aralkyl, c1-C10 acyl or if pa or p> 0, addl. a group OR27; R25 = R27 = R27 = H, PG; R5 = H, substituted alkyl, aryl or aralkyl, (GH2)sT s= 1-4, T = OR22 or halogen; R6, R7 = H or together = bond or 0; G = X=GR8 or bi- or tricyclic The antitumor agents, 6-alkenyl-, 6-alkynyl- and 6-spoxyspothilones I (Rla, Rlb are same or different = H, Cl-ClO alkyl, C6-Cl2 aryl, C7-C20 aralkyl each optionally substituted; or together = (CH2)m m = 1-5 or '-CH2OCH2-; R2a(R2b 9

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= 0, two OR23 groups, C2-C10-1kyłene-cz,o-dloxy straight chain or branched; H/OR9 or CRIORII group and R23 = alkyl radical, R9 = H, PG, R10,R11 = same or different = H, substituted alkyl, radical, R9 = H, PG, R10,R11 = same or methylene are a 5-7 carbocyclic ring; D-E = CH2CH2 or OCH2, A = OCH2, CH2C(0), NR29C(0), NR29C2 and R29 = H, alkyl; Z = O or H/OR12 and R12 = H, PG) were prepared flus II was prepared in a multistep synthesis starting from (45)-4-(2-methyl-1-cxoprop-2-yl)-2,2- dimethyl[1,3]dioxane and 5- trimethylsilylpent-4-in-1-yl magnesium bromide. II had an IC50 value [nM] of 3.0 for the growth inhibition of Human MCF-7 breast—and 75 for multidrug resistant NIT/ADR carcinoma call lines with a selectivity of 2.5. The new epothilone derivs, interact with tubulin by stabilizing microtubuli that are with the need for cell growth, division and/or proliferation. Thus the epothlion derives are suitable for treating malignant tumors, e.g., ovarian, stomach, colon, adeno-, breast, lung, head and neck carcinomas, malignant melanoma, acute lymphocytic and myelocytic leukemia; and for anti-anglogenesis aryl radical and R8 = H, halogen, CN, or substituted alkyl, aryl or aralkyl; X formed. They are able to influence the cell-splitting in a phase-specific manner and are therefore useful in treating diseases or conditions associated therapy as well as for treatment of chronic inflammatory diseases (such as psoriasis, arthritis).

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

REFERENCE COUNT:

SSW T T T T T T T T T T T T T T T T T T	ACCESSION NUMBER: 2000:772379 CAPLUS FULL-text ACCESSION NUMBER: 2000:772379 CAPLUS FULL-text DOCUMENT NUMBER: 2000:772379 CAPLUS FULL-text TITLE: 6-Alkenyl and 6-alkymyl derivatives of epothilone INTENTOR(S): Stubells, Neares: Buchmann, Barnd; Hoffmann, Jens: Lichtner, Rosemarie Schering AG., Germany CODNENT TYPE: Cerrann CODNENT TYPE: Cerrann Patent CAPLUS ACC. NUM. COUNT: 3 PATENT NEORWATION:	KIND DATE APPLICATION NO.	3203 T 20021217 JP 2000-615619 568 A 20030217 EE 2001-568 A 20040227 NZ 2000-514989 B2 20040506 AU 2000-43103
ANGERNA WOODE CAN WOOD CAN	ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: INVENTOR(S): PATENT ASSIGNEE(S): SOUNCE: DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COPATENT INFORMATION:	FENT NO. 19921086 2371226 200006658 W: AE, CU, LV, SG, CG, CG, CG, CG, CG, CG, CG, CG, CG, C	

SN 10/563058 Page 11 of 172 STIC STN SEARCH RESULTS

Subcellular distribution of epothilones in human tumor Lichtner, R. B.; Rotgeri, A.; Bunte, T.; AUTHOR(S): TITLE:

Research Laboratories of Schering AG, Berlin, 13342, Buchmann, B.; Hoffmann, J.; Schwode, R.; Skuballa, W.; Klar, U. CORPORATE SOURCE:

Proceedings of the National Academy of Sciences of the United States of America (2001), 98(20), 11743-11748 CODEN: PNASA6; ISSN: 0027-8424 Germany

SOURCE:

National Academy of Sciences

Journal

analogs, 6-propyl-bpoB (pEB) and 6-propyl-bpoD (pED), in comparison with the natural compds. EpoB/EpoD, by using human A431, MCF7, and MDR1-overexpressing NCI/Adr cells. By using tritiated pEB/pED, compound uptake, release, and nuclear accumulation were investigated in A431 and NCI/Adr cells. In these cells, epothilones can principally be recognized and exported by verapamil-sensitive efflux pumps, which are not identical to MDR1. The degree of export nM, resp., was increased in the presence of 10 µM Verapamil in both cell lines 2- to 8-fold. In contrast, the intracellular levels of pEB were affected by Verapamil only at 3.5 nM pEB in NCl/Adr (2-fold) and not in A431 cells. In pacificated or pED (5-15%) in both cell lines. Our study suggests that differences in growth inhibitory efficacy between epoxide and olefin analogs may be based on different mechanisms of drug accumulation and subcellular Epothilones are a new class of natural and potent antineoplastic agents that stabilize microtubules. Although 12,13-epoxide derivs. are potent antiproliferative agents, the activities of the corresponding 12,13-olefin analogs are significantly decreased. These data were confirmed for two new depends on the structure, olefin vs. apoxide-analog, and also on the intracellular drug concentration The accumulation of pED used at 3.5 or 70 addition, strong nuclear accumulation was observed for pEB (40-50%) but not English DOCUMENT TYPE: LANGUAGE: AB Epothilone

THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT 34

135:236394 Synthesis of radioactively labeled epothilone derivatives and their biochemical and pharmaceutical 2001:676638 CAPIUS Full-text CAPLUS L102 ANSWER 11 OF 24 ACCESSION NUMBER: DOCUMENT NUMBER:

Merner; Schwede, Wolfgang; Buchmann, Bernd; Bunte, Thomas; Lichtner, Klar, Ulrich; Gay, Juergen; Skuballa,

INVENTOR(S):

Schering Aktiengesellschaft, Germany PCT Int. Appl., 31 pp. CODEN: PIXXD2 Rosemarie PATENT ASSIGNEE(S):

German Patent FAMILY ACC. NUM. COUNT: PATENT INFORMATION: DOCUMENT TYPE: LANGUAGE: SOURCE:

2 E B 20010309 유 본 보 구 કે કે ડે £,4,5 APPLICATION NO. WO 2001-EP2699 FI, KR, ¥,8,6, X 黑 X 20010913 AC, KE, AM, AT, DK, DM, IS, JP, KIND AE, AG, AL, I CR, CU, CZ, I ID, IL, IN, I WO 2001066154 PATENT NO.

SN 10/563058 Page 12 of 172 STIC STN SEARCH RESULTS

, BE, CH, CY, ; SE, TR, BF,), TG A 20000309 **ដ**់វ g, S 5, ₹ PT, US, 77, 70, , SZ, TZ, UG, ZW, 7 , IT, LU, MC, NL, 6 , ML, MR, NE, SN, 1 DE 2000-10013363 PL, UG, MW, MX, MZ, NO, NZ, TM, TR, TT, TZ, UA, MARPAT 135:236394 មិន្ MK, MN, SL, 13, 9 8 K ₹£.ξ SK, ងុដុព្ MA, MD, SG, SI, ZW G, ES, PRIORITY APPLA. INFO.: មិនទី OTHER SOURCE(S): GI SA, SB, 3

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The invention relates to novel radioactively labeled pharmacol. effective epothilone derivs. of general formula (I), where RI represents O-FG and hydroxyl, where PG is a protective group; R2b are the same or different and represent, independent of one another, hydrogen CI-CIO alkyl, aryl, C7-C20 aralkyl or, together, represent a GHZ)m group, where m is equal to 1, 2, 3, 4 or 5; R3 represents a C2-CIO alkyl group, where m is equal to 1, 2, 3, 4 or 5; R3 represents a C2-CIO alkyl group, where m equals 1 or 2; R4 represents O-FG and hydroxyl, R5 represents hydrogen, CI-CIO alkyl, aryl, C7-CZO aralkyl and halogen; W2 represents a C42-CH2, CH2-O or O-CH2 group; R6 represents hydrogen, C1-CIO alkyl, aryl, C7-CZO aralkyl, (GR2)s-V and halogen, Where s equals 1, 2, 3 at 4 and V represents Protection of CH2) by the CA10 alkyl, aryl, R6 secth represent a hydrogen atom and, together, represent an addnl. bond or an oxygen atom; A represents artl, G7-G20 artalkyl, and a group R10-G1-G2-, where R9 represents hydrogen, halogen, GN, G1-G20 alkyl, aryl, and G7-G20 aralkyl, and R10 represents hydrogen, G1-G20 alkyl-, aryl-, G7-G20 aralkyl, and X-Y The novel compds. of represents an O-C(=0), an O-CH2, a CH2-C(=0), an NR11-C(=0) and an NR11-S02 group, wherein R11 represents hydrogen and C1-C10 alkyl. The novel compdes formula I are valuable pharmaceuticals and valuable diagnostic probes for elucidating, for example, active mechanisms and biochem. pharmacokinetic and/or pharmacodynamic processes.

Preparation of 6-alkenyl-, 6-alkynyl- and 6-epoxyepothlione derivatives and their antitumor activity CAPLUS COPYRIGHT 2007 ACS on STN 2000:790507 CAPLUS Full-text 133:362656 L102 ANSWER 12 OF 24 ACCESSION NUMBER: DOCUMENT NUMBER: INVENTOR(S):

Schering Aktiengesellschaft, Germany PCT Int. Appl., 298 pp. Skuballa, Werner; Buchmann, Bernd; Klar, Ulrich; Schwede, Wolfgang; Jens; Lichtner, Hoffmann, PATENT ASSIGNEE(S): SOURCE:

CODEN: PIXXD2 DOCUMENT TYPE: LANGUAGE:

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Oxa-epothilones, such as I [83 = heteroaryl, heteroarylalkenyl, heteroarylalones, corarylalones, between the state of the

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L102 ANSWER 9 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:780370 CAPLUS FULL-text
DOCUMENT NUMBER: 135:331294
TITLE: Preparation of epothilone derivatives for pharmaceutical use in the treatment of cancer INVENTOR(S): Brochaman, Bernel Rat, ULIACh; Stuballa, Farner: Schede, Folfgang; Hoffmann, Jens; Lichtner, Rosemarie Schering A.-G., Germany
SOURCE: CODEN: GAYKEK
DOCUMENT TYPE: Patent
LANGAAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

		KT#00007	20010419
APPLICATION NO.		DE 2000-1002031/	WO 2001-EP4552
DATE		2011002	20011101
KIND	;	¥ :	AZ
PATENT NO.	100000111111111111111111111111111111111	DE 1002031/	WO 2001081342

SN 10/563058 Page 10 of 172 STIC STN SEARCH RESULTS

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MARPAT 135:331294

OTHER SOURCE(S): GI

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AB Epothilones, such as I [R3 = heteroaryl, heteroarylalkenyl, R8R8a = alkylene, heteroarylahoalkenyl,ecc.; R8, R8a = H, alkyl, alkynyl; R8R8a = bond, O; R16 = H, GN, alkyl, alkynyl; R1R16a = bond, O; R16 = H, GN, alkyl, halogen; X = O, NH; X1 = O, CH3], were prepared for a variety of therapeutic uses, such as treatment of malignant tymors, proliferative diseases, leukemia, and chronic inflammetory diseases. Proliferative propared via a multistep synthetic sequence starting from (3S)-dihydro-3-hydroxy-4,4-dimethyl-2(3H)-furanone, L-(-)-malic acid, and [(2-methyl-4-thazolyl)methyl]phosphonic acid di-Et ester. Pharmacoutical formulations of the prepared oar-epothilones were discussed, but specific biol. activity data was not presented.

LIO2 ANSWER 10 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN ACESSION NUMBER: 2001:729040 CAPLUS Full-text DOCUMENT NUMBER: 136:95676

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SN 10/563058 Page 7 of 172 STIC STN SEARCH RESULTS

Schering Aktiengesellschaft, Germany Bernd; Schwede, Wolfgang; PCT Int. Appl., 30 pp. CODEN: PIXXD2 Skuballa, Werner Patent German FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PATENT ASSIGNEE(S): DOCUMENT TYPE: LANGUAGE: SOURCE:

20021223 CA, CH, CN, GE, GH, GM, LK, LR, LS, OM, PH, PL, TT, TZ, UA, AM, AZ, BY, DK, EE, ES, TR, BF, BJ, TG 20021223 20021223 20011221 20021223 20011221 ZW, DE, SK, TD, DE 2001-10164592 AU 2002-356783 US 2002-326263 DE 2001-10164592 WO 2002-EP14758 CASREACT 139:85166; MARPAT 139:85166 SZ, ZX, 8.E 8 6 APPLICATION NO. SZ, TZ, UG, BG, CH, CY, NL, PT, SE, ML, MR, NE, វ ខ SI, Ş SL, BE, MC, GW, 8648848488 20030709 AU, DM, IS, SE, SE, TM, IT, K, ₹ _₹ ង្គ ន្ ន្ 5,5,5,6,6,0 PRIORITY APPLN. INFO.: 3 8 5 8 g DE 10164592 AU 2002356783 US 2003176710 WO 2003053949 Ä OTHER SOURCE(S): 8 PATENT NO. RW: g

C1-10-alkyl, aryl O-benzylation with PhGH2Br, hydroboration with BH3-THF complex, dehydrotetrahydropyranylation- isopropylidenation with Me2C(OMe)2 in MeCOMe containing catalytic tosyl acid, hydrogenolytic debenzylation, Swern oxidation, Grignard reaction with MeMgBr, oxidn, with TPAT in GH2C12 contg, NOmethylmorpholine N-oxide and alkylation with allyl bromide.

3 THERE ARE 3 THERE ARE 3 THERE PRE REPUSES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT The invention relates to C1-C6 fragments I [Rla, Rlb = H, REFERENCE COUNT Ą

SN 10/563058 Page 8 of 172 STIC STN SEARCH RESULTS

Synthesis and biological activity of epothilones Klar, Ulrich; Skuballa, Werner; Buchmann, Barnd; Schwede, Wolfgang; LIO2 ANSWER 7 OF 24 CAPLUS COPYRICHT 2007 ACS on STN ACCESSION NUMBER: 2002:132142 CAPLUS FULL-text ACCESSION NUMBER: DOCUMENT NUMBER: AUTHOR(S):

Germany ACS Symposium Series (2001), 796(Anticancer Agents),

Bunte, Thomas; Hoffmann, Jens; Lichtner, Rosemarie B. Research Laboratories of Schering AG, Berlin, D-13342,

CORPORATE SOURCE:

A review. The total synthesis and biol. activity of epothilone analogs are described. Selected SAR data indicate the possibility to improve activity and selectivity by structural modifications. The new compds. may help to elucidate the therapeutic potential of this class of anticancer drugs. RENCE COUNT:

16 THERE ARE 16 CITED REFERENCES ANAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT CODEN: ACSMC8; ISSN: 0097-6156 American Chemical Society Journal; General Review English DOCUMENT TYPE: PUBLI SHER: LANGUAGE: 9

on STN L102 ANSWER 8 OF 24 CAPLUS COPYRIGHT 2007 ACS on ACCESSION NUMBER: 2001;780372 CAPLUS <u>Full</u> 135:331295 DOCUMENT NUMBER:

REFERENCE COUNT:

pharmaceutical use in the treatment of cancer Schwede, Wolfgang; Klar, Ulrich; Preparation of oxa-epothilone derivatives for Skuballa, Warner; Buchmann, Barnd; INVENTOR(S): TITLE:

Hoffmann, Jens; Lichtner, Rosemarie Schering A.-G., Germany Ger. Offen., 46 pp. CODEN: GWXXEX Patent PATENT ASSIGNEE(S): DOCUMENT TYPE: SOURCE:

German FAMILY ACC. NUM. COUNT: PATENT INFORMATION: LANGUAGE:

20000420 <u> ያ</u> ቜ ጛ ዼ ጛ ¥ 5.5 × ER, GH, DE 2000-10020899 WO 2001-EP4551 APPLICATION NO. 18 KB 83, BB, FI, KR, TT, Ä,Ĕ RS, 20011025 20011101 20020425 EE, AU, DZ, 高美芸 81, 94, St, St, St, KIND A1 A2 AM, DK, DK, MG, AE, AG, AL, AG, CR, CR, CL, ID, IL, IN, IN, IV, MA, MD, N SE, SG, SI, SA, ZA, ZW, AE DE 10020899 WO 2001081341 WO 2001081341 PATENT NO.

THE REST OF THIS BIB INFORMATION WAS NOT AVALLABLE AT THE TIME OF PRINTING (DOWNLOADING INTERRUPTED)

SN 10/563058 Page 5 of 172 STIC STN SEARCH RESULTS

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active ingredients II [AK = OC(:0), OCH2, CH2C(:0), NR29C(:0), NR29SO2; R29 = H, C1-6-alkyl] according to known methods. The invention also relates to the corresponding C1-C12 fragments.

REFERENCE COUNT:

1 THERE ARE 1 CITED REFERENCES ANAILABLE FOR THIS
                                                                                                                                                                        THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORWAT
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Use of epothilones in the treatment of brain diseases associated with proliferative processes Lichtner, Rosemarie; Rotgeri, Andrea; Klar, Ulzich; Hoffmann, Jens; Buchmann, Barnd; Schwede, Rolfgang; Skuballa, US COPYRIGHT 2007 ACS on STN 2003:719306 CAPLUS Full-text 139:240340 Schering A.-G., Germany PCT Int. Appl., 53 pp. CODEN: PIXXD2 English 2 Merzier Patent L102 ANSWER 4 OF 24 CAPLUS LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PATENT ASSIGNEE(S): ACCESSION NUMBER: DOCUMENT NUMBER: DOCUMENT TYPE: INVENTOR(S): SOURCE: TITIE:

CA, CH, CM, GD, GE, GH, LC, LK, LR, NZ, OM, PH, TT, TZ, UA, AM, AZ, BY, DK, EE, ES, SK, TR, BF, SE, MC, PT, HU, SK GR, IT, LI, LU, NL, SE, MC, PT, AL, TR 20030228 20030228 20030228 20030228 20030228 Ę SN, TD, A1 20030912 CA 2003-2477403 A1 20030916 AU 2003-215618 A1 20041201 EP 2003-743360 B2, DK, ES, FR, GB, GR, IT, LI, LU, NI, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, ZW, DE, L, SZ, TZ, UG, ZM, Z E, BG, CH, CY, CZ, E J, MC, NL, PT, SE, S S, GW, ML, MR, NE, S EP 2002-4745 EP 2002-4745 US 2002-361062P WO 2003-EP2085 Ά, BR 2003-8154 JP 2003-572570 MX 2004-PA8450 NO 2004-4175 APPLICATION NO. 2003-EP2085 SZ, ZW SZ, BG, MC, I છે CI, CM, GA, GN, G Al 20030903 DE, DK, ES, FR, G LV, FI, RO, MK, C 20050713 20030912 ξ, ξ, 20050104 20050825 AI, DE, 5,3 IV, 'MA KIND Ğ,Ğ R: AT, BE, CH, IE, SI, LT, ₩. हें इ PRIORITY APPLN. INFO.: GM, HR, H 115, LT, L 12, LT, L 13, LT, L 14, LT, L 15, LT, L 16, LS, L 17, L 18, C 1 R: AT, BE, IE, SI, BR 2003008154 JP 2005525360 MX 2004PA08450 NO 2004004175 8, AG, GR, GR, CA 2477403 AU 2003215618 EP 1480643 WO 2003074053 PATENT NO.

OTHER SOURCE(S):

AB The invention provides the use of an Epothilone, which shows an average distribution coefficient between plasma and brain of 0.3 to 1.5 in the mouse i.v. bolus injection assay, for the preparation of a medicament for the treatment of a brain disease associated with proliferative processes.

10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE FOR PROPARAT

L102 ANSWER 5 OF 24 CAPLUS COPYRIGHT 2007 ACS on STN

139:85166
Method for producing C1-C6 fragments of epothilones and the derivatives thereof RIar, Ulrioh; Berger, Markus; Buchmann,

INVENTOR (S): TITLE:

SN 10/563058 Page 6 of 172 STIC STN SEARCH RESULTS

2003:693140 CAPLUS Full-text

ACCESSION NUMBER:

ACCESSION NUMBER:	2003:693140 CAPLUS FULL-text
TITLE:	Use of epothilones in the treatment of brain diseases
INVENTOR(S):	sr, Rosemarie; Rotgeri,
	Bornd; Hoffmann, Karin; Klar, Ulrich; Schwode, Wolfgang; Skuballa, Werner
PATENT ASSIGNEE (S):	Schering Aktiengesellschaft, Germany
SOURCE:	Eur. Pat. Appl., 27 pp. Coden: EPXXDM
DOCUMENT TYPE:	
	English
FAMILY ACC. NUM. COUNT: PATENT INFORMATION:	
PATENT NO.	KIND DATE APPLICATION NO. DATE
EP 1340498	20030903 EP 2002-4745
R: AT, BE,	DK, ES, FR, GB, GR, IT, LI, LU, NL, SE
IE,	CY, AL, TR
	20030912 CA 2003-2477403
3074053	20030912 WO 2003-EP2085 200302
W: AE, AG, AL,	AM, AI, AU, AZ, BA, BB, BG, BK, BI, BZ, CA, CH, CN, CT, DE DY, DY, DY, EC, EE, ES, EI, CB, CP, CF, CU
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ફેં	MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
2	TJ, TM, AT, BE, BG, CH, CY; CZ, DE, DK, EE,
FI, FR, GB,	IE, IT, LU, MC, NL, PT, SE,
•	CM, GA, GA, GQ, GW, ML, MK, NE, SN, IU,
	AU 2003-21361B
•	20041201 EP 2003-743360
R: AT,	DK, ES, FR, GB, GR, IT, LI, LU, NL, SE
	RO, MK, CY, AL, TR, BG, CZ, EE,
200300815	20050104 BR 2003-8154
	20050803 CN 2003-809761
	20050825 JP 2003-572570
	20050713 MX 2004-PA8450
	20041201 NO 2004-4175
2004007	2004-7905
PRIORITY APPLN. INFO.:	2002-4745 A
	2002-361062P P
	WO 2003-EP2085
ÄÄ	MARPAT 139:191465
AB The invention provi	٠,
bolus injection ass	u
of a brain disease	
REFERENCE COUNT:	10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS BECORD ALL CITATIONS AVAILABLE IN THE DE CORMAT
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1102 ANSWER 6 OF 24 CAPLUS	US COPYRIGHT 2007 ACS on STN 2003-511314 CAPIUS Full-text.
DOCUMENT NUMBER:	
77775	Method for producing C1-C6 fragments of enothilones

SN 10/563058 Page 3 of 172 STIC STN SEARCH RESULTS

LANGUAGE: OTHER SOURCE(S): DOCUMENT TYPE:

English CASREACT 142:355075



COPYRIGHT 2007 ACS on STN :29293 CAPLUS Full-text 2005:29293 CAPLUS 142:113814 CAPLUS L102 ANSWER 3 OF 24 ACCESSION NUMBER: DOCUMENT NUMBER:

Method for producing C1-C15 fragments of epothilones and derivatives thereof
Klar, Ulrich; Buchmann, Barnd;
Schwede, Wolfgang; Skuballa, Merner INVENTOR (S): TITLE:

Schering Aktiengesellschaft, Germany PCT Int. Appl., 48 pp. CODEN: PIXXD2 German Patent LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PATENT ASSIGNEE(S): DOCUMENT TYPE: SOURCE:

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SN 10/563058 Page 4 of 172 STIC STN SEARCH RESULTS

NO 2006-554 US 2006-563058 DE 2003-10331004 WO 2004-EP6685 20060403 20070621 A I US 2007142675 PRIORITY APPLN. INFO.: NO 2006000554

OTHER SOURCE(S):

20060619 20030703 20040619 CASREACT 142:113814; MARPAT 142:113814

The invention relates to a method for preparing C1-C15 fragments I [R1a, R1b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R1aR1b = (GH2)m; m = 2 - 5; R2a, R2b = H, C1-10-alkyl, C2-10-alkenyl, C2-10-alkyl, aryl, C7-20-aralkyl; R2aR2b = (GH2)n; n = 2 - 5; R3 = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4a, R4b = = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4aRdb = (GH2)p; p = 2 - 5; R5 = H, C1-10-alkyl, aryl, C7-20-aralkyl; R6, R7 = H; R6R7 = bond, O; G = X:CRB, bi- or tricyclic aryl; R8 = H, halogen, (un)substituted C1-20-alkyl, aryl, C7-20-

9

aralkyl; X = 0, (0R23)2, C2-10-akkylane a, andioxy, H(OR9), CRIGHI; R23 = C1-20-akkyl; R9 = H, protecting group; R10, R11 = H, C1-10-alkyl, aryl, C7-20-aralkyl; CR10R11 = 5 - to 7-membered carbocyele; R13 = CH20R13a, CH2-halo, CG, C2R13b, CG-halo; R13a, R14a = H, S02alkyl, S02-aryl, S02-aralkyl; R13aR14a = (CH2)o, CR15aR15b; o = 2 - 4; R13b, R14b = H, C1-10-alkyl; R15a, R15b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R15a, R15b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R15a, R15b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R15a, R15b = Goothilones and derive. The proceedure comprises the bonding of a C1-C6 fragment, R13CH2CHR14CR1aR1bC(:0)CHR2aR2b, to a C7-C12 fragment,

RSC(:V)(CH2)3CR46AR40C(:W)R3a [V, W = 0, (OR23)2, CZ=10=alkylane= a, w-dioxy, H(OR9)], to form a CI-C12 fragment, RSC(:V)(CH2)3CR46R40CR3a(0-PG1-C12) fragment, G-CR20'CH2CRY) [FI = H, proreacting group], which is then treated with a CI3-C15 fragment, G-CR20'CH2CRY) R21 [RY] = H; R20' = h10goon, N3, NHR29, OH, O-PG, NR29-PG, CI-20-(perfluoro)alkylsulfonyloxy, (CI-4-alkyl, NO2, CI, B-rabstituted) banzyloxy, NR29502Me, NR39C(:O)Me, R21 = OH, halo, O-PG, P+PhHal = F, CI, Br, I), P(O)(OQ)2 (Q = CI-10-alkyl, Ph), P(:O)PD2; R29 = H, CI-6-alkyl], to form the CI-C15 sporthine intermediate product I. Thus, I [R1a = R1b = R5 = Me, R2a = CH2CH:CH2-B, R2b

delsopropylidenation/defetrabydropy ranylation with catalyric 4-MeC6H4SO3H in EtOH, silylation with CF3SO2SiMe2CMe3, regioselective deallylation with (1)-camphor-10- sulfonic acid, Swern oxidation with DMSO/(COC1)2 in CH2C12 and β , R20 = OSiMe2CMe3-a, G = 2-methylbenzothiazol-5- yl, PG = SiMe2CMe3, Z = O] was prepared from (S)-4-(2-methyl-3-oxohept-6-en- 2-yl)-2,2-dimethyl-1,3-= R4b = H-α, R3 = H-β, R4a = Me-β, R6R7 = bond, R13 = CO2H, R14 = OSiMe2CMe3catalytic tetrapropylammonium perruthenate, Wittig reaction with [(3S)-3-(2-Bu4NF in THF, oxidation in CH2Cl2 containing N-methylmorpholine N-oxide and butyldimethylsilyl)oxylheptanal, tetrahydropyranylation, desilylation with carbonyl oxidation with NaOC12 in aqueous THF/Me3COH. The produced C1-C15 epothilone intermediate products can be converted into the intrinsically dioxane via lithiation and reaction with (2S,6RS)-2-methyl-6-[(tertmethylbenzothiazol-5- yl)propyl|triphenylphosphonium lodide,

SN 10/563058 Page 1 of 172 STIC STN SEARCH RESULTS

-> file registry ILE 'REGISTRY' ENTERED AT 12:11:27 ON 11 OCT 2007 USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT. PLEASE SEE "HELP USAGETERMS" FOR DETAILS. COPYRIGHT (C) 2007 American Chemical Society (ACS) Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem

HIGHEST RN 950149-06-1 HIGHEST RN 950149-06-1 10 OCT 2007 10 OCT 2007 STRUCTURE FILE UPDATES: DICTIONARY FILE UPDATES: New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA : INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches BEGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

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16 FILE COVERS 1907 - 11 Oct 2007 VOL 147 ISS 1 FILE LAST UPDATED: 10 Oct 2007 (20071010/ED) Effective October 17, 2005, revised CAS Information Use Policies apply. They are available for your review at:

http://www.cas.org/infopolicy.html d stat que L100 î

L91 AND L92 AND L93 AND L94 KLAR U?/AU BUCHMANN B?/AU SCHWEDE W?/AU. SKUBALLA W?/AU PLU=ON PLU=ON PLU=ON PLU=ON PLU=ON 80 SEA FILE-CAPLUS ABB-ON
116 SEA FILE-CAPLUS ABB-ON
60 SEA FILE-CAPLUS ABB-ON
186 SEA FILE-CAPLUS ABB-ON
24 SEA FILE-CAPLUS ABB-ON 1.91 1.92 1.93 1.94 1.102

SN 10/563058 Page 2 of 172 STIC STN SEARCH RESULTS

=> => d ibib abs L102 tot

Total synthesis and antitumor activity of ZK-EPO: The first fully synthetic epothilon9 in clinical Germany Schering AG, Research Center Eurpoe, Berlin, Ger Angewandte Chemie, International Edition (2006), Hoffmann, Jens; Lichtner, Rosemarie B. development
Klar, Ulrich; Buchmann, Bernd;
Schwede, Wolfgang; Skuballa, Werner; Wiley-VCH Verlag GmbH & Co. KGaA 2006:1337456 CAPLUS Full-text 146:229070 45(47), 7942-7948 CODEN: ACIEF5; ISSN: 1433-7851 COPYRIGHT 2007 ACS on STN English CASREACT 146:229070 CAPLUS L102 ANSWER 1 OF 24 ACCESSION NUMBER: DOCUMENT NUMBER: TITLE: CORPORATE SOURCE: SOURCE: LANGUAGE: OTHER SOURCE(S): PUBLISHER: DOCUMENT TYPE: AUTHOR(S):

efficacy than taxanes, such as paclitaxel and second-generation epothilones, fast and efficient cellular uptake, no recognition by efflux mechanisms, and an improved therapeutic window.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS From about 350 active epothilone analogs synthesized by a highly convergent synthesis, ZK-EPO (I) was chosen for clin. development on the basis of its outstanding preclin. data. This compound exhibits higher activity and 9

THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Efficient chiral pool synthesis of the C1-C6 fragment Klar, Ulrich; Roehr, Bodo; Kuczynski, Frank; Schwede, Wolfgang; Berger, Markus; 2005:132732 CAPLUS Full-text COPYRIGHT 2007 ACS on STN of epothilones 142:355075 CAPLUS L102 ANSWER 2 OF 24 ACCESSION NUMBER: DOCUMENT NUMBER: AUTHOR(S): TITLE:

Research Laboratories of Schering AG, Berlin, 13342, Skuballa, Werner; Buchmann, Bernd CORPORATE SOURCE:

301-305 CODEN: SYNTBF; ISSN: 0039-7881 Georg Thieme Verlag Synthesis (2005), (2), PUBLI SHER: SOURCE:

SN 10/563058 Page 68 of 69 STIC STN SEARCH RESULTS

D STAT QUE L19

FILE 'BABS' ENTERED AT 15:47:02 ON 11 OCT 2007 D STAT QUE L14

FILE 'ZCAPLUS, BEILSTEIN, BABS' ENTERED AT 15:47:21 ON 11 OCT 2007
L25

25 DUP REM L6 L19 L14 (7 DUPLICATES REMOVED)

ANSWERS '1-18' FROM FILE ZCAPLUS

ANSWERS '19-25' FROM FILE BEILSTEIN

D IBIB ABS HITSTR L25 1-18
D IDE ALLREF L25 19-25

FILE HOME

FILE STNGUIDE :

FILE CONTAINS CURRENT INFORMATION.

LAST RELOADED: Oct 5, 2007 (20071005/UP).

FILE REGISTRY

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 10 OCT 2007 HIGHEST RN 950149-06-1 DICTIONARY FILE UPDATES: 10 OCT 2007 HIGHEST RN 950149-06-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

FILE ZCAPLUS

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FILE COVERS 1907 - 11 Oct 2007 VOL 147 ISS 16 FILE LAST UPDATED: 10 Oct 2007 (20071010/ED)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d his full (FILE 'HOME' ENTERED AT 15:09:07 ON 11 OCT 2007) FILE 'STNGUIDE' ENTERED AT 15:22:34 ON 11 OCT 2007 FILE 'REGISTRY' ENTERED AT 15:31:01 ON 11 OCT 2007 STRUCTURE UPLOADED L1L20 SEA SSS SAM L1 L3 SCREEN 1008 0 SEA SSS SAM L1 AND L3 68 SEA SSS FUL L1 AND L3 SAVE TEMP LAO058STR1CL/A L5 FILE 'ZCAPLUS' ENTERED AT 15:37:30 ON 11 OCT 2007 18 SEA ABB=ON PLU=ON L5 L6 E US2006-563058/APPS 1 SEA ABB=ON PLU=ON US2006-563058/AP D SCA 1 SEA ABB=ON PLU=ON L6 AND L7 - L8 D SCA FILE 'BEILSTEIN' ENTERED AT 15:40:57 ON 11 OCT 2007 0 SEA SSS SAM L1 L9 L100 SEA SSS SAM L1 AND L3 38 SEA SSS FUL L1 AND L3 L1126 SEA ABB=ON PLU=ON L11/COM L12 5 SEA ABB=ON PLU=ON L12 AND BABSAN/FA L13 SEL BABSAN FILE 'BABS' ENTERED AT 15:42:39 ON 11 OCT 2007 7 SEA ABB=ON PLU=ON (6300090/BABSAN OR 6630563/BABSAN OR L146085475/BABSAN OR 6376421/BABSAN OR 6410256/BABSAN OR 6473119/B ABSAN OR 6597156/BABSAN) FILE 'BEILSTEIN' ENTERED AT 15:43:07 ON 11 OCT 2007 21 SEA ABB=ON PLU=ON L12 NOT L13 14 SEA ABB=ON PLU=ON L15 AND RN/FA L15 L16 FILE 'REGISTRY' ENTERED AT 15:43:45 ON 11 OCT 2007 L17 14 SEA ABB=ON PLU=ON L5 AND BEILSTEIN/LC NOT CAPLUS O SEA ABB=ON PLU=ON L5 AND BEILSTEIN/LC NOT CAPLUS/LC L18 FILE 'BEILSTEIN' ENTERED AT 15:44:11 ON 11 OCT 2007 L197 SEA ABB=ON PLU=ON L15 NOT L16 252 SEA ABB=ON PLU=ON KLAR U?/AU L20 351 SEA ABB=ON PLU=ON BUCHMANN B?/AU 436 SEA ABB=ON PLU=ON SCHWEDE W?/AU L22 L23 369 SEA ABB=ON PLU=ON SKUBALLA W?/AU

0 SEA ABB=ON PLU=ON L19 AND (L20 OR L21 OR L22 OR L23)

FILE 'REGISTRY' ENTERED AT 15:46:28 ON 11 OCT 2007

D-COST

FILE 'ZCAPLUS' ENTERED AT 15:46:31 ON 11 OCT 2007 D STAT QUE L6

FILE 'BEILSTEIN' ENTERED AT 15:46:51 ON 11 OCT 2007

and the company

SN 10/563058 Page 66 of 69 STIC STN SEARCH RESULTS

Field Availability:

Code	Name Occurre	nce
=======		==
BRN	Beilstein Records	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	3
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO.	Beilstein Citation	1
DED	Entry Date	1
DUPD	Update Date	1
NMR	Nuclear Magnetic Resonance	1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
========		=========
RX [°]	Reaction Documents	1
RXPRO	Substance is Reaction Product	1

All References:

ALLREF

1. Aberhart et al., J.Chem.Soc.Perkin Trans.1, CODEN: JCPRB4, <1974>, 816,823

SN 10/563058 Page 65 of 69 STIC STN SEARCH RESULTS

<u> </u>		====
BRN	Beilstein Records	1
CN	Chemical Name	1
AUN	Autonomname	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	6
FS	File Segment	1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
BSO	Beilstein Citation ""	1
DED	Entry Date	1
DUPD	Update Date	1.
CDER	Chemical Derivative	1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
		_======================================
RX .	Reaction Documents	1
RXPRO:	Substance is Reaction Product	· 1

All References:

ALLREF

1. Fehr, T. et al., J.Chem.Soc.Perkin Trans.1, CODEN: JCPRB4, <1974>, 836-847

L25 ANSWER 25 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN): 1677640 C40 H60 D2 O21 Molec. Formula (MF): 880.93 Molecular Weight (MW): 17586, 1155, 680 Lawson Number (LN): File Segment (FS): Stereo compound heterocyclic Compound Type (CTYPE): Constitution ID (CONSID): 1560573 Tautomer ID (TAUTID): 1638549 Beilstein Citation (BSO): 1988/11/30 Entry Date (DED): 1990/02/07 Update Date (DUPD):

SN 10/563058 Page 64 of 69 STIC STN SEARCH RESULTS

RX Reaction Documents

1 RXPRO Substance is Reaction Product 1

All References:

ALLREF

 Aberhart et al., J.Chem.Soc.Perkin Trans.1, CODEN: JCPRB4, <1974>, 816,823

L25 ANSWER 24 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN): 1677845

Chemical Name (CN): 2-butyl-18-(3,4-dimethoxy-5-methoxymethyl-

> tetrahydro-furan-2-yloxy)-32-hydroxy-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-

dimethyl-tritriacont-16-enoic acid

1-(2-hydroxy-1-methyl-ethyl)-3-methoxy-2methyl-6-(N, N', N'-trimethyl-quanidino)-

hexyl ester

2-butyl-18-(3,4-dimethoxy-5-methoxymethyl-Autonom Name (AUN):

tetrahydro-furan-2-yloxy)-32-hydroxy-

3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-

dimethyl-tritriacont-16-enoic acid

Occurrence

1-(2-hydroxy-1-methyl-ethyl)-3-methoxy-2methyl-6-(N,N',N'-trimethyl-guanidino)-

hexyl ester

C71 H139 N3 O19 Molec. Formula (MF):

Molecular Weight (MW): 1338.89

17586, 3238, 2817, 2294, 1762, 289 Lawson Number (LN):

File Segment (FS): Stereo compound heterocyclic Compound Type (CTYPE):

Constitution ID (CONSID): 1561576 Tautomer ID (TAUTID): 1636624 5-17 Beilstein Citation (BSO):

1988/11/30 Entry Date (DED): Update Date (DUPD): 1991/03/25

Field Availability:

Code Name

SN 10/563058 Page 63 of 69 STIC STN SEARCH RESULTS

1. Chakraborty, T. K.; Dutta, S., Tetrahedron Lett., CODEN: TELEAY, 39(1-2), <1998>, 101-104; BABS-6085475

L25 ANSWER 23 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN): 1965671 heptadecane-1, 3, 5, 7, 9, 11, 16-heptaol Chemical Name (CN): heptadecane-1, 3, 5, 7, 9, 11, 16-heptaol Autonom Name (AUN): Molec. Formula (MF): C17 H36 O7 Molecular Weight (MW): 352.47 687 Lawson Number (LN): Compound Type (CTYPE): acyclic Constitution ID (CONSID): 1838397 Tautomer ID (TAUTID): 1903620 Beilstein Citation (BSO): 5-01 1989/06/29 Entry Date (DED): 1997/12/03 Update Date (DUPD):

Field Availability:

Marian de la companya de la company La companya de la co

Code	Name	Occurrence			
BRN	Beilstein Records		1		
BPR	Beilstein Preferred RN		1		
RN	CAS Registry Number		1		
CN	Chemical Name	. 1 - 1	1		
AUN	Autonomname	•	1		
MF	Molecular Formula		1		
FW	Formular Weight		1		
LN	Lawson Number		1		
CTYPE	Compound Type		1		
CONSID	Constitution ID		1		
TAUTID	Tautomer ID		1		
BSO	Beilstein Citation		1 .		
DED	Entry Date		1		
DUPD	Update Date		1		
IR	Infrared Spectrum		1		
MP	Melting Point		1		
MS	Mass Spectrum		1		

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
========		

- 120 July 2 July 200 Comment

SN 10/563058 Page 62 of 69 STIC STN SEARCH RESULTS

Chemical Name (CN): 12-benzyloxy-7-(tert-butyl-dimethylsilanyloxy)-3-hydroxy-4,4,6,8-tetramethyl-5-oxo-dodecanoic acid tert-butyl ester 12-benzyloxy-7-(tert-butyl-dimethyl-Autonom Name (AUN): silanyloxy)-3-hydroxy-4,4,6,8-tetramethyl-5-oxo-dodecanoic acid tert-butyl ester Molec. Formula (MF): C33 H58 O6 Si Molecular Weight (MW): 578.90 5228, 3798, 3777, 2672, 318 Lawson Number (LN): File Segment (FS): Stereo compound Compound Type (CTYPE): isocyclic 6834281 Constitution ID (CONSID): Tautomer ID (TAUTID): 7583399 Beilstein Citation (BSO): 6-06 Entry Date (DED): 1998/11/09 Update Date (DUPD): 1998/11/09

Field Availability:

Name	Occurrence
Reilstein Records	1
Chemical Name	1
Autonomname	. 1
Molecular Formula	. 1
Formular Weight	1
Lawson Number	. 5
File Segment	1
Compound Type	1
Constitution ID	1
Tautomer ID	1
Beilstein Citation	1
Entry Date	.1
Update Date	1
	Beilstein Records Chemical Name Autonomname Molecular Formula Formular Weight Lawson Number File Segment Compound Type Constitution ID Tautomer ID Beilstein Citation Entry Date

This substance also occurs in Reaction Documents:

Code	<u>N</u> ame	an in the		:	Occurrence
=====		========		=	*******
RX	Reaction	Documents	•		.2
RXREA	Substance	is Reacti	on Reactan	ī.	1
RXPRO	Substance	is Reacti	on Product		. 1

All References:

ALLREF

Field Availability:

Code	Name	Occurrence
======	=======================================	
BRN	Beilstein Records	1
CN	Chemical Name	1
AUN	Autonomname	. 1
MF	Molecular Formula	1
FW	Formular Weight	. 1
LN	Lawson Number	3
FS	File Segment	. 1
CTYPE	Compound Type	1
CONSID	Constitution ID	1
TAUTID	Tautomer ID	1
DED	Entry Date	1
DUPD	Update Date	1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
=======		
RX	Reaction Documents	2
RXREA	Substance is Reaction Reactant	1
RXPRO	Substance is Reaction Product	1

All References: ALLREF

- Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 - 1948; BABS-6591064
- 2. Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron-Lett., CODEN: TELEAY, 45(9), <2004>, 1945 1948; BABS-6441824;

L25 ANSWER 22 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN):

7955235

Field Availability:

Code ·	Name	Occurren	ıce
========		=======	==
BRN .	Beilstein Records		1
CN ·	Chemical Name		1
AUN	Autonomname		1
·MF	Molecular Formula		1
FW	Formular Weight	•	1.
LN	Lawson Number		4
FS ·	File Segment		1
CTYPE	Compound. Type		1
CONSID	Constitution ID		1
TAUTID	Tautomer ID		1
DED	Entry Date		1
DUPD	Update Date		1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
=======		========
RX	Reaction Documents	2
RXREA	Substance is Reaction Reactant	. 1
RXPRO	Substance is Reaction Product	. 1

All References: ALLREF

- Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 - 1948; BABS-6591064
- Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 - 1948; BABS-6441824

L25 ANSWER 21 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN):	9738862
Chemical Name (CN):	3,7-bis-(tert-butyl-dimethyl-silanyloxy)-
	4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid
Autonom Name (AUN):	3,7-bis-(tert-butyl-dimethyl-silanyloxy)-
	4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic
	acid
Molec. Formula (MF):	C29 H58 O6 Si2
Molecular Weight (MW):	558.94
Lawson Number (LN):	3798, 3777, 2674
File Segment (FS):	Stereo compound
Compound Type (CTYPE):	acyclic
Constitution ID (CONSID):	8203590
Tautomer ID (TAUTID):	9128603
<pre>Entry Date (DED):</pre>	2004/10/23
Update Date (DUPD):	2007/02/05

SN 10/563058 Page 59 of 69 STIC STN SEARCH RESULTS

CTYPE	Compound Type	1
CONSID	Constitution ID	. 1
TAUTID	Tautomer ID	1
DED	Entry Date	1
DUPD	Update Date	1

This substance also occurs in Reaction Documents:

Code	Name	Occurrence
========		-
RX	Reaction Documents	2
RXREA	Substance is Reaction Reactant	1
RXPRO	Substance is Reaction Product	1

All References:

ALLREF

- Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 - 1948; BABS-6591064
- 2. Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.; Petryka, Joseph; Liu, Fenghua; Myles, David C., Tetrahedron Lett., CODEN: TELEAY, 45(9), <2004>, 1945 1948; BABS-6441824

L25 ANSWER 20 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN): 9738952 3,7-bis-(tert-butyl-dimethyl-silanyloxy)-Chemical Name (CN): 4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid methyl ester 3,7-bis-(tert-butyl-dimethyl-silanyloxy)-Autonom Name (AUN): 4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid methyl ester C30 H60 O6 Si2 Molec. Formula (MF): 572.97 Molecular Weight (MW): 3798, 3777, 2674, 289 Lawson Number (LN): File Segment (FS): Stereo compound Compound Type (CTYPE): acyclic Constitution ID (CONSID): 8203696 Tautomer ID (TAUTID): 9128457 2004/10/23 Entry Date (DED): 2007/02/05 Update Date (DUPD):

L25 ANSWER 19 OF 25 BEILSTEIN COPYRIGHT 2007 BEILSTEIN MDL on STN

Beilstein Records (BRN): 9747518 Chemical Name (CN): 3,7-bis-(tert-butyl-dimethyl-silanyloxy)-4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid 2-methyl-3-(2-methyl-thiazol-4-yl)-1-(2-oxo-ethyl)-allyl ester 3,7-bis-(tert-butyl-dimethyl-silanyloxy)-Autonom Name (AUN): 4,4,6,8-tetramethyl-5,12-dioxo-tridecanoic acid 2-methyl-3-(2-methyl-thiazol-4-yl)-1-(2-oxo-ethyl)-allyl ester C39 H69 N O7 S Si2 Molec. Formula (MF): Molecular Weight (MW): 752.21 Lawson Number (LN): 31322, 3798, 3777, 2674 File Segment (FS): Stereo compound Compound Type (CTYPE): heterocyclic Constitution ID (CONSID): 8211765 Tautomer ID (TAUTID): 9136618 Entry Date (DED): 2004/10/23 Update Date (DUPD): 2007/02/05

Field Availability:

Code	Name	Occurrence
=======		
BRN	Beilstein Records	1
CN	Chemical Name	1
AUN	Autonomname	1
MF	Molecular Formula	1
FW	Formular Weight	1
LN	Lawson Number	4
FS	File Segment	1

SN 10/563058 Page 57 of 69 STIC STN SEARCH RESULTS

Absolute stereochemistry.

RN 53294-58-9 ZCAPLUS

CN 1,2,3,5,7,9,11,16-Heptadecaneoctol (9CI) (CA INDEX NAME)

RN 53294-63-6 ZCAPLUS

CN 1,2,3,5,7,9,11,16-Heptadecaneoctol, octaacetate (9CI) (CA INDEX NAME)

RN 53294-64-7 ZCAPLUS

CN: 1,3,5,7,9,14-Pentadecanehexol (9CI) (CA INDEX NAME)

RN 53294-65-8 ZCAPLUS

CN 1,3,5,7,9,14-Pentadecanehexol, hexaacetate (9CI) (CA INDEX NAME)

RN 53294-66-9 ZCAPLUS

CN 1,3,5,7,9,11,16-Heptadecaneheptol, heptaacetate (9CI) (CA INDEX NAME)

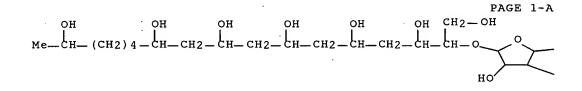
SN 10/563058 Page 56 of 69 STIC STN SEARCH RESULTS

- The structures of secopyrimycins A [MeO2CCHBuCH(OH)CHMe(CH2)2[CH(OH)(CH2)3]2[CH(OH)]2Me], B (I), and C, [AcNH(CH2)3[CH(OH)CHMe]2 CH2OH] were detd.from their high resolution mass spectra and/or those of their simplederivs. and chemical degradation products.
- IT 54799-27-8

RL: PRP (Properties)

(mol. structure of, mass spectrum in relation to)

- RN 54799-27-8 ZCAPLUS
- CN 1,3,5,7,9,11,16-Heptadecaneheptol, 2-(α -D-arabinofuranosyloxy)-(9CI) (CA INDEX NAME)



PAGE 1-B

____CH2-OH

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L25 ANSWER 18 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1974:437769 ZCAPLUS Full-text

DOCUMENT NUMBER:

81:37769

TITLE:

Constitution of primycin. I. Characterization,

functional groups, and degradation to the

secoprimycins

AUTHOR(S):

Aberhart, John; Jain, Rup C.; Fehr, Theo; De Mayo,

Paul; Szilagyi, Imre

CORPORATE SOURCE:

Dep. Chem., Univ. West. Ont., London, ON, Can.

SOURCE:

Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999)

(1974), (7), 816-26

CODEN: JCPRB4; ISSN: 0300-922X

DOCUMENT TYPE:

Journal English

LANGUAGE:

GI

For diagram(s), see printed CA Issue.

AB The proposed structure of primycin (I) was determined mainly from the chemical and spectral data-of its degradation products.

IT 53294-56-7P 53294-58-9P 53294-63-6P 53294-64-7P 53294-65-8P 53294-66-9P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of)

RN 53294-56-7 ZCAPLUS

CN 1,3,5,7,9,11,16-Heptadecaneheptol, 2-[(2,3,5-tri-O-acetyl- α -D-arabinofuranosyl)oxy]-, heptaacetate (9CI) (CA INDEX NAME)

SN 10/563058 Page 55 of 69 STIC STN SEARCH RESULTS

arabinofuranosyl)oxy]-, 6-[[(dimethylamino)iminomethyl]methylamino]-1-(2-hydroxy-1-methylethyl)-3-methoxy-2-methylhexyl ester, monohydrochloride (9CI) (CA INDEX NAME)

PAGE 1-A

HC1

PAGE 1-B

L25 ANSWER 17 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1974:436929 ZCAPLUS Full-text

DOCUMENT NUMBER:

81:36929

TITLE:

Constitution of primycin. II. Mass spectra of the

secoprimycins

AUTHOR(S):

Gracey, D. E. Fergus; Baczynskyj, Lubomir; Martin,

Trevor I.; MacLean, David B.

CORPORATE SOURCE:

Dep. Chem., McMaster Univ., Hamilton, ON, Can.

SOURCE:

Journal of the Chemical Society, Perkin Transactions

1: Organic and Bio-Organic Chemistry (1972-1999)

(1974), (7), 827-36

CODEN: JCPRB4; ISSN: 0300-922X

DOCUMENT TYPE:

Journal

LANGUAGE:

English

GI For diagram(s), see printed CA Issue.

PAGE 1-B

∼ОМе

RN 53294-05-6 ZCAPLUS

CN 16-Tritriacontenoic acid, 2-butyl-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-dimethyl-32-oxo-18-[(2,3,5-tri-O-methyl- α -D-arabinofuranosyl)oxy]-, methyl ester (9CI) (CA INDEX NAME)

PAGE 1-A

PAGE 1-B

RN 53294-53-4 ZCAPLUS

CN α-D-Arabinofuranoside, 2,4,6,8,10-pentamethoxy-15-(methoxy-d3)-1-(methoxy-d3-methyl)hexadecyl 2,3,5-tri-0-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 53503-23-4 ZCAPLUS

CN 16-Tritriacontenoic acid, 2-butyl-32-hydroxy-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-dimethyl-18-[(2,3,5-tri-O-methyl- α -D-

SN 10/563058 Page 53 of 69 STIC STN SEARCH RESULTS

RN 53294-03-4 ZCAPLUS

CN 16-Tritriacontenoic acid, 32-(acetyloxy)-2-butyl-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-dimethyl-18-[(2,3,5-tri-O-methyl- α -D-arabinofuranosyl)oxy]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-B

~OMe

RN 53294-04-5 ZCAPLUS

CN 16-Tritriacontenoic acid, 2-butyl-32-hydroxy-3,7,11,15,19,21,23,25,27-nonamethoxy-4,16-dimethyl-18-[(2,3,5-tri-O-methyl- α -D-arabinofuranosyl)oxy]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.

Double bond geometry unknown.

SN 10/563058 Page 52 of 69 STIC STN SEARCH RESULTS

DOCUMENT TYPE:

Journal

LANGUAGE:

English

GI For diagram(s), see printed CA Issue.

AB Methylation of primycin (I) gave, after chromatog., the trimethylated urea and guanidine derivs. (II and III). The structure of I was determined by a spectral study of the ozonolysis products of II and III and their degradation products.

IT 53293-97-3P 53293-98-4P 53293-99-5P 53294-00-1P 53294-03-4P 53294-04-5P 53294-05-6P 53294-53-4P 53503-23-4P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of)

RN 53293-97-3 ZCAPLUS

CN α-D-Arabinofuranoside, 15-hydroxy-1-(hydroxymethyl)-2,4,6,8,10-pentamethoxyhexadecyl 2,3,5-tri-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 53293-98-4 ZCAPLUS

CN α -D-Arabinofuranoside, 15-(acetyloxy)-1-[(acetyloxy)methyl]-2,4,6,8,10-pentamethoxyhexadecyl 2,3,5-tri-O-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 53293-99-5 ZCAPLUS

CN 1,2,16-Heptadecanetriol, 3,5,7,9,11-pentamethoxy- (9CI) (CA INDEX NAME)

RN 53294-00-1 ZCAPLUS

CN Hexadecanal, 15-hydroxy-2,4,6,8,10-pentamethoxy- (9CI) (CA INDEX NAME)

SN 10/563058 Page 51 of 69 STIC STN SEARCH RESULTS

RN. 197634-37-0 ZCAPLUS

CN 4,15-Dioxa-3,16-disilaoctadecan-7-one, 5-(2-hydroxyethyl)-2, 2, 3, 3, 6, 6, 8, 10, 17, 17-decamethyl-16, 16-diphenyl-9-(phenylmethoxy)- $[5S-(5R^*,8S^*,9R^*,10R^*)]-(9CI)$ (CA INDEX NAME)

Absolute stereochemistry.

RN 197634-39-2 ZCAPLUS

Dodecanoic acid, 3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-12-[[(1,1-CN dimethylethyl)diphenylsilyl]oxy]-4,4,6,8-tetramethyl-5-oxo-7-(phenylmethoxy)-, [3S-(3R*,6S*,7R*,8R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L25 ANSWER 16 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

1974:463919 ZCAPLUS Full-text

DOCUMENT NUMBER:

81:63919

TITLE:

Constitution of primycin. III. Degradation of methylated primycin, and the structure of primycin Fehr, Theo; Jain, Rup C.; De Mayo, Paul; Motl, O.;

AUTHOR (S):

Szilagyi, Imre; Baczynskyj, Lubomir; Gracey, D. E. Fergus; Holland, Herbert L.; MacLean, David B.

CORPORATE SOURCE:

Dep. Chem., Univ. West. Ont., London, ON, Can.

SOURCE:

Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry (1972-1999)

(1974), (7), 836-47

CODEN: JCPRB4; ISSN: 0300-922X

SN 10/563058 Page 50 of 69 STIC STN SEARCH RESULTS

RN 197634-31-4 ZCAPLUS

CN 3-Decanone, 2-(2,2-dimethyl-1,3-dioxan-4-yl)-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,4,6-trimethyl-5-(phenylmethoxy)-,
[4S-[4R*(4S*,5R*,6R*)]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 197634-33-6 ZCAPLUS

CN 5-Dodecanone, 12-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-1,3-dihydroxy-4,4,6,8-tetramethyl-7-(phenylmethoxy)-, [3S-(3R*,6S*,7R*,8R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 197634-35-8 ZCAPLUS

CN 4,17-Dioxa-3,18-disilaeicosan-9-one, 7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,2,3,3,8,8,10,12,19,19-decamethyl-18,18-diphenyl-11-(phenylmethoxy)-, [7S-(7R*,10S*,11R*,12R*)]- (9CI) (CA INDEX NAME)

SN 10/563058 Page 49 of 69 STIC STN SEARCH RESULTS

IT 197634-28-9P 197634-29-0P 197634-30-3P 197634-31-4P 197634-33-6P 197634-35-8P 197634-37-0P 197634-39-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(intermediates in the total synthesis of epothilones A and B)

RN 197634-28-9 ZCAPLUS

CN 3-Decanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-hydroxy-2,4,6-trimethyl-, (4R,5S,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 197634-29-0 ZCAPLUS

CN 3-Decanone, 2-(2,2-dimethyl-1,3-dioxan-4-yl)-10-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,4,6-trimethyl-5-(phenylmethoxy)-, [4S-[4R*(4S*,5R*,6R*)]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 197634-30-3 ZCAPLUS

CN 3-Decanone, 2-(2,2-dimethyl-1,3-dioxan-4-yl)-10-hydroxy-2,4,6-trimethyl-5-(phenylmethoxy)-, [4S-[4R*(4S*,5R*,6R*)]]- (9CI) (CA INDEX NAME)

SN 10/563058 Page 48 of 69 STIC STN SEARCH RESULTS

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                                             US 1999-344713
                                                                 A3 19990625
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OTHER SOURCE(S):

CASREACT 127:346234

GΙ

Intermediates, e.g. 2-(2,2-dimethyl-1,3-dioxan-4-yl)-2-methyl-3-pentanone, 6-AB [(tert-butyldimethylsilyl)oxy]-2-methylhexanal, (S,4E)-3-benzyloxy-1- (tertbutyldimethylsilyloxy)-4-methyl-5-(2-ethyl-thiazol-4-yl)-4-pentene (I), (4S,6S)-10(tert-butyldimethylsilyloxy)-2-(2,2-dimethyl-1,3-dioxan-4-yl)-5hydroxy-2,4,6-trimethyl-3-decanone (II) and (3S,6R,7S,8S)-7-benzyloxy-3-(tert-butyldimethylsilyloxy)-12-(tert-butyldiphenylsilyloxy)-4,4,6,8tetramethyl-5-oxododecanoic acid, in the total synthesis of epothilones A and B are described. Epothilones A and B are natural products,. IT197634-08-5P

RL: PNU (Preparation, unclassified); PREP (Preparation) (intermediates in the total synthesis of epothilones A and B)

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RN197634-08-5 ZCAPLUS

CN Dodecanoic acid, 12-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3,7-dihydroxy-4,4,6,8-tetramethyl-5-oxo-, methyl ester, $[3S-(3R^*,6S^*,7R^*,8R^*)]-(9CI)$ (CA INDEX NAME)

The title compds. [I; II; III; R1, R2 = H, alkyl, aryl, aralkyl; R3 = CH2OH, AΒ CH2OR; R4 = OH, OR; R = CR7R8; R7, R8 = H, alkyl, aryl, or R7R8 = (CH2)n; n = 2-6; R5, R6 = H, alkyl, aralkyl, or R5R6 = (CH2)m; m = 2-5; R9, R10 = H, protecting group; R11 = H, protecting group] including all the stereoisomers and their mixts. are prepared E.g., title compound (S)-III [R5 = R6 = Me, R9 = R11 = H, R10 = TBDPS] was prepared in 6 steps from D-(-)-pantolactone via reaction with 3,4-dihydro-2H-pyran, hydride reduction, Wittig reaction with methyltriphenylphosphonium bromide, protection of OH with TBDPS-Cl, detetrahydropyranyl, and reduction with borane-THF.

197634-28-9P IT

> RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of new C1-C6-fragments and application for synthesis of epothilone and epothilone derivs.)

RN197634-28-9 ZCAPLUS

3-Decanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-4)-4]-10-[(1,1-4)-4CN dimethylethyl)dimethylsilyl]oxy]-5-hydroxy-2,4,6-trimethyl-, (4R,5S,6S)-(CA INDEX NAME)

Absolute stereochemistry.

L25 ANSWER 15 OF 25 ACCESSION NUMBER:

ZCAPLUS COPYRIGHT 2007 ACS on STN 1997:708545 ZCAPLUS

Full-text

DOCUMENT NUMBER:

127:346234

TITLE:

Intermediate products within the total synthesis of

Epothilones A and B

INVENTOR(S):

Schinzer, Dieter; Limberg, Anja; Boehm, Oliver M.

Schering A.-G., Germany

SOURCE:

Ger., 14 pp.

CODEN: GWXXAW

DOCUMENT TYPE:

Patent

LANGUAGE:

German

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PATENT ASSIGNEE(S):

PATENT NO.						KINI)	DATE		APPLICATION NO.						DATE			
							-												
	DE	1963	6343			ci		1997	1023]	DE 1	996-	1963	6343		19	9960	330	
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SN 10/563058 Page 46 of 69 STIC STN SEARCH RESULTS

TITLE:

New (C1-C6)-fragments, method for their preparation and their application for synthesis of epothilone and

epothilone derivatives

INVENTOR(S):

Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner;

Buchmann, Bernd; Schirner, Michael

PATENT ASSIGNEE(S):

Schering A.-G., Germany Ger. Offen., 18 pp.

SOURCE:

CODEN: GWXXBX

DOCUMENT TYPE:

Patent

LANGUAGE:

German

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

PAT	PATENT NO.					KIND DATE			APPLICATION NO.									
	19735										1997-:							
CA	22996	8.0			A1		19990	0218		CA	1998-2	2299	608		1	9980	810	
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WO	99076	92			A3		1999	0514										
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$$R^{3}$$
 R^{4}
 R^{1}

Ι

SN 10/563058 Page 45 of 69 STIC STN SEARCH RESULTS

Absolute stereochemistry.

RN 220774-78-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-4-(phenylmethyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4S,5R,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-80-1 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-8-(phenylmethyl)-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7R,8S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. --

L25 ANSWER 14 OF 25 ACCESSION NUMBER:

ZCAPLUS COPYRIGHT 2007 ACS on STN 1999:116659 ZCAPLUS <u>Full-text</u> 130:168164

SN 10/563058 Page 44 of 69 STIC STN SEARCH RESULTS

RN 220774-61-8 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-4-(phenylmethyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-62-9 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-8-(phenylmethyl)-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-76-5 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-4-(phenylmethyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

SN 10/563058 Page 43 of 69 STIC STN SEARCH RESULTS

Absolute stereochemistry.

RN 220774-58-3 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(phenylmethyl)-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-59-4 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(phenylmethyl)-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-60-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-4-(phenylmethyl)-5[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

SN 10/563058 Page 42 of 69 STIC STN SEARCH RESULTS

Absolute stereochemistry.

RN 220774-21-0 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-22-1 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-4-ethyl-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-23-2 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-8-ethyl-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

SN 10/563058 Page 41 of 69 STIC STN SEARCH RESULTS

melanoma, and acute lymphocytic and myelocytic leukemia. They are also suited for anti-angiogenesis therapy and for the treatment of chronic inflammatory diseases (psoriasis, arthritis). To prevent uncontrolled cell growth on, and for better tolerability of, medical implants, the derivs. can be introduced into or applied to polymeric materials. The compds. provided for in the invention can be used alone or, to achieve additive or synergistic effects, in combination with other principles and substance categories used in tumor therapy.

IT 220775-76-8

RL: RCT (Reactant); RACT (Reactant or reagent) (preparation of epothilone derivs. as antitumor agents)

RN 220775-76-8 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,8,10-trimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 220774-19-6P 220774-20-9P 220774-21-0P 220774-22-1P 220774-23-2P 220774-58-3P 220774-59-4P 220774-60-7P 220774-61-8P 220774-62-9P 220774-76-5P 220774-78-7P 220774-80-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

. -.. 31.1

(preparation of epothilone derivs. as antitumor agents)

RN 220774-19-6 ZCAPLUS

CN 3-Undecanone, 2-[(4s)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4R,5s,6s)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-20-9 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

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SN 10/563058 Page 40 of 69 STIC STN SEARCH RESULTS

DE	1973	5575			A1	1	.999(0211	DE	1	L997-	1973	5575			19	9708	309
DE	1973	5578			A1	1	.9990	0211	DE	1	L997-	1973	5578			19	9708	309
DE	1974	8928			A1	1	9990	0429	DE	1	L997-	1974	8928			19	9710	024
DE	1974	9717			A1	1	9990	0506	DE	1	L997-	1974	9717			19	971	031
DE	1975	1200			A1	1	.999(0520	DE	1	L997-	1975	1200			19	971:	L13
DE	1981	3821			A1	1	.9990	0923	DE	1	L998-	1981	3821			19	9803	320
CA	2299	608			A1	1	.9990	0218	CA	. 1	L998-	2299	608			19	9808	310
AU	9893	409			Α	1	.9990	0301	AU	1	L998-	9340	9		•	19	9808	310
EP.	1005	465			A2	.2	0000	0607	EP	1	L998-	9463	09			19	9808	310
EP	1005	465			B,1	2	2007	0725										
	R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB, G	R,	IT,	LI,	LU,	NL,	SI	Ξ,	MC,	PT,
		IE,	SI,	LT,	LV,	FI,	RO,	CY,	AL, M									
JP.	2001	51272	23		T	· 2	2001	0828	JP	2	2000-	5061	96			19	980	310
ZA	9810	403			Α		0000	0515			L998-					19	981	113
IN	1908	05			A1			0823		1	L998-	DE34	13				981	
	2003				A1			0731			2000-						000	
	2002				Α	2	20050	0311			2002-						0212	
PRIORITY	Y APP	LN.	INFO	.:							L997-				Α		970	
											L997-				Α		970	
											L997-				A		970	
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											1997-				A		971	
											1997-				A		971	
											L998-				A		980	
									WO)]	1998-	EP50	64		W	19	980	3 T O

OTHER SOURCE(S):

MARPAT 130:196529

R2?

AB Epothilone derivs. of formula I $[X = 0, alkylene-\alpha, \omega-dioxy, two alkoxy groups,$ etc.; Y = O, H2; Z = O, (H, OH), (H, protected OH); Rla, Rlb = H, alkyl, aryl, aralkyl, or together = (CH2)m where m = 2, 3, 4, 5; R2a, R2b = H, alkyl, aryl, aralkyl, or together = (CH2)n where n = 2, 3, 4, 5; when D-E = CH2CH2 or when Y = O, R2a or R2b may not be H/Me; R3 = H, alkyl, aryl, aralkyl; R4a, R4b = H, alkyl, aryl, aralkyl, or together = (CH2)p where p = 2, 3, 4, 5; D-E = CH2CH2,CH:CH, C.tplbond.C, 2,3-oxiranediyl, CH(OH)CH(OH), CH(OH)CH2; R5 = H, alkyl, aryl, aralkyl; R6, R7 = H, together = a saturated bond or O; R8 = H, alkyl, Thus, the title compas. (4S,7R,8S,9S,13E,16S(E)) - and (4S,7R,8S,9S,13Z,16S(E))-4,8-dihydroxy-7- ethyl-16-(1-methyl-2-(2-methyl-4-thiazolyl) ethenyl)-1-oxa-5,5,9,13tetramethylcyclohexadec-13-en-2,6-dione (II) were prepared in many steps. The new compds. interact with tubulin by stabilizing formed microtubuli. They are capable of influencing cell division in a phase-specific manner and are suitable for the treatment of malignant tumors, such as ovarian, gastric, colon, breast, lung, head and neck carcinoma, adenocarcinoma, malignant

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RN 220774-23-2 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-8-ethyl-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L25 ANSWER (13 OF 25) 2

ZCAPLUS COPYRIGHT 2007 ACS on STN 1999:126888 ZCAPLUS Full-text

ACCESSION NUMBER:

130:196529

TITLE:

Preparation of new epothilone derivatives as

pharmaceutical agents

INVENTOR(S):

Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner;

Buchmann, Bernd; Schirner, Michael

PATENT ASSIGNEE(S):

Schering Aktiengesellschaft, Germany

SOURCE:

DOCUMENT TYPE:

Patent

CODEN: PIXXD2

LANGUAGE:

German

FAMILY ACC. NUM. COUNT:

German

PATENT INFORMATION:

PAT	CENT	NO.			KIN	D :	DATE		Ġ	APPL	ICAT:	ION I	NO.		D	ATE	
						-											
WO	9907	692		•	A2		1999	0218	1	WO 1	998-	EP50	64		1	9980	310
WO	9907	692			A3		1999	0514									
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		EE,	·ES,	FI,	GB,	GE,	GΗ,	GM,	HU,	ID,	IL,	IS,	JP,	KE,	KG,	KP,	KR,
		ΚZ,	LC,	LK,	LR,	LS,	LT,	LU,	LV,	MD,	MG,	MK,	MN,	MW,	MX,	NO,	NZ,
		PL,	PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	ТJ,	TM,	TR,	TT,	UA,	UG,
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	RW:	GH,	GM,	ΚE,	LS,	MW,	SD,	SZ,	UG,	ZW,	AT,	BE,	CH,	CY,	DE,	DK,	ES,
		FI,	FR,	GB,	GR,	ΙE,	IT,	LU,	MC,	NL,	PT,	SE,	BF,	ВJ,	CF,	CG,	CI,
		CM,	GA,	GN,	GW,	ML,	MR,	NE,	SN,	TD,	TG						
DE	1973	5574			A1		1999	0211		DE 1	997-	1973	5574		1	9970	809

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SN 10/563058 Page 38 of 69 STIC STN SEARCH RESULTS

RN 220774-20-9 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-21-0 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-22-1 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-4-ethyl-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Ι

New epothilone derivs. I (Rla, Rlb = R2a, R2b = same or different H, alkyl, AB aryl, aralkyl or (CH2)m,n m, n = 2-5; R3 = H, alkyl, aryl, aralkyl; R4a,R4b =same or different H, alkyl, aryl, aralkyl or (CH2)p = 2-5, CH2CH2, CH=CH, C.tplbond.C, epoxy, CH(OH)CH(OH), CH(OH)CH2; D-E = a group; R5 = H, alkyl, aryl, aralkyl; R6,R7 = H, bond, O; R8 = H, alkyl, aryl, aralkyl; X = O, OR23alkylene- α ,- ω -dioxy group straight or branched, OR9 or the CR10R11 group where R23 = alkyl, R9 = H or protecting group and R10, R11 = same or different H. alkyl, aryl, aralkyl or R10,R11 = together with methylene are a 5-7 membered carbocyclic ring; Y = O or two H; Z = O or H/OR12 and R12 = H or a protecting group) were prepared Thus E- and Z-II were prepared via a multistep synthesis. I cooperate with tubulin by stabilizing formed microtubuli. able phase specifically to affect the cell division and are suitable for the treatment of malignant ovarian, stomach, colon, adeno, breast, lung, head and neck tumors, malignant melanomas, acute lymphocytic and myelocytic leukemia. Derivs. of I are suitable for use in anti-angiogenic therapy as well as for treating chronic inflammatory diseases (psoriasis, arthritis). *Incorder to prevent uncontrolled cell proliferations and to improve the compatibility of medical implants I can be applied or incorporated into polymeric materials. I can be used alone or to achieve additive or synergistic effects in combination with further principles and substance classes applicable in tumor therapy. ΙT

220774-19-6P 220774-20-9P 220774-21-0P

220774-22-1P 220774-23-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of new epothilone derivs. and their pharmaceutical uses)

RN 220774-19-6 ZCAPLUS

CN

3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4R, 5S, 6S) - (9CI) (CA INDEX NAME)

SN 10/563058 Page 36 of 69 STIC STN SEARCH RESULTS

Absolute stereochemistry.

303154-57-6P ΙT

> RL: SPN (Synthetic preparation); PREP (Preparation) (6-alkenyl and 6-alkynyl derivs. of epothilone)

303154-57-6 ZCAPLUS RN

3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-CN dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L25 ANSWER 12 OF 25

ZCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2000:738730 ZCAPLUS Full-text

DOCUMENT NUMBER:

133:309795

TITLE: Preparation of new epothilone derivatives and their

pharmaceutical uses

Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; INVENTOR(S):

Buchmann, Bernd; Schirner, Michael

PATENT ASSIGNEE(S): Schering A.-G., Germany

SOURCE: Ger. Offen., 74 pp.

CODEN: GWXXBX Patent DOCUMENT TYPE:

German LANGUAGE:

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

	•			
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19908767	A1	20001019	DE 1999-19908767	19990218
PRIORITY APPLN. INFO.:			DE 1999-19908767	19990218
OTHER SOURCE(S):	MARPAT	133:309795		
GT				

SN 10/563058 Page 35 of 69 STIC STN SEARCH RESULTS

RN 303154-58-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-59-8 ZCAPLUS

CN 3-Undecanone, 4-(3-butynyl)-2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-60-1 ZCAPLUS

CN 2,9-Undecanedione, 8-(3-butynyl)-10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

SN 10/563058 Page 34 of 69 STIC STN SEARCH RESULTS

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            CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,
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            LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE,
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    MX 2001PA11039
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    US 2005113429
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                                            IN 2005-MN837
                                                                    20050802
     IN 2005MN00837
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                                20070608
                                20060302
                                            US 2005-214988
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     US 2006046997
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PRIORITY APPLN. INFO .:
                                            DE 1999-19921086
                                            DE 1999-19954228
                                                                A 19991104
                                            DE 2000-10013363
                                                                A 20000309
                                            DE 2000-10015836
                                                                A 20000327
                                                                A3 20000501
                                            JP 2000-615619
                                            WO 2000-IB657
                                                                W 20000501
                                            IN 2001-MN1305
                                                                A3 20011019
                                            US 2002-979939
                                                                A3 20020606
OTHER SOURCE(S):
                         MARPAT 133:321769
AΒ
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The title compds. were prepared by various combinations of 3 fragments making up the mols. Thus, [4S,7R,8S,9S,13Z,16S(E)]-4,8-dihydroxy-16-[1- methyl-2-(2-pyridyl)ethenyl]-1-oxa-5,5,9,13-tetramethyl-7-(3-butynyl)-13- cyclohexadecene-2,6-dione was prepared in several steps starting from (4S)-4-(2-methyl-1-oxo-2-propyl)-2,2-dimethyl[1,3]dioxane and 5-(trimethylsilyl)-4-pentynylmagnesium bromide.

IT 303154-56-5P 303154-58-7P 303154-59-8P 303154-60-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(6-alkenyl and 6-alkynyl derivs. of epothilone)

RN 303154-56-5 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

SN 10/563058 Page 33 of 69 STIC STN SEARCH RESULTS

Absolute stereochemistry.

IT 303154-57-6P

RL: SPN (Synthetic preparation); PREP (Preparation) (preparation of 6-alkenyl-, 6-alkynyl- and 6-epoxyepothilone derivs. and their use in pharmaceutical prepns.)

303154-57-6 ZCAPLUS RN

3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dioxan-4-yl]-10-[(1,1-diCN dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 11 OF 25

ACCESSION (NUMBER:

DOCUMENT NUMBER:

TITLE:

SOURCE:

INVENTOR(S):

PATENT ASSIGNEE(S):

ZCAPLUS COPYRIGHT 2007 ACS on STN

2∕000:772379 ZCAPLUS Full-text 133:321769

6-Alkenyl and 6-alkynyl derivatives of epothilone Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner;

Buchmann, Bernd; Hoffmann, Jens; Lichtner, Rosemarie

Schering A.-G., Germany

Ger. Offen., 18 pp.

CODEN: GWXXBX

DOCUMENT TYPE:

LANGUAGE:

Patent German

FAMILY ACC. NUM. COUNT:

3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19921086	A1	20001102	DE 1999-19921086	19990430
CA 2371226	A1	20001109	CA 2000-2371226	20000501
WO 2000066589	A1	20001109	WO 2000-IB657	20000501

SN 10/563058 Page 32 of 69 STIC STN SEARCH RESULTS

RN 303154-58-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-59-8 ZCAPLUS

CN 3-Undecanone, 4-(3-butynyl)-2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-60-1 ZCAPLUS

CN 2,9-Undecanedione, 8-(3-butynyl)-10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

SN 10/563058 Page 31 of 69 STIC STN SEARCH RESULTS

DE 1999-19954228 A1 19991104 DE 2000-10015836 A1 20000327 DE 2000-10013363 Α 20000309 WO 2000-IB657 W 20000501 IN 2001-MN1305 A3 20011019 US 2002-979939 A3 20020606

OTHER SOURCE(S):

MARPAT 133:362656

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

The antitumor agents, 6-alkenyl-, 6-alkynyl- and 6-epoxyepothilones I (R1a, R1b are same or different = H, C1-C10 alkyl, C6-C12 aryl, C7-C20 aralkyl each optionally substituted; or together = (CH2)m m = 1-5 or -CH2OCH2-; R2a(R2b replace a with b) = H, substituted alkyl, aryl, aralkyl, (CH2)ra-C.tplbond.(or =)C-(CH2)pa-R26a, Q, Q1 where n = 0-5; ra, rb = the same or different and = 0-4; pa, pb = the same or different and = 0-3; R3a = H, substituted alkyl, aryl or aralkyl; R3b = OH, OPG14; R14 = H, OR14a, halogen and R14a = H, SO2-alkyl, SO2-aryl or SO2-aralkyl; R4 = H, substituted alkyl, aryl or aralkyl; halogen, OR25, CN; R26a, R26b = same or different = H, substituted alkyl, aryl or aralkyl, C1-C10 acyl or if pa or pb > 0, addnl. a group OR27; R25 = R27 = R22 = H, PG; R5 = H, substituted alkyl, aryl or aralkyl, (CH2) sT s = 1-4, T = OR22 or halogen; R6, R7 = H or together = bond or O; G = X=CR8 or bi- or tricyclic aryl radical and R8 = H, halogen, CN, or substituted alkyl, aryl or aralkyl; X = 0, two OR23 groups, C2-C10-alkylene- α , ω -dioxy straight chain or branched; H/OR9 or CR10R11 group and R23 = alkyl radical, R9 = H, PG, R10,R11 = same or different = H, substituted alkyl, aryl or aralkyl, or together with the methylene are a 5-7 carbocyclic ring; D-E = CH2CH2 or OCH2; A = OC(O), OCH2, CH2C(0), NR29C(0), NR29S02 and R29 = H, alkyl; Z = O or H/OR12 and R12 = H, PG) were prepared Thus II was prepared in a multistep synthesis starting from (4S)-4-(2-methyl-1-oxoprop-2-yl)-2,2-dimethyl[1,3]dioxane and 5trimethylsilylpent-4-in-1-yl magnesium bromide. II had an IC50 value [nM] of 3.0 for the growth inhibition of human MCF-7 breast- and 75 for multidrug resistant NCI/ADR carcinoma cell lines with a selectivity of 2.5. The new epothilone derivs. interact with tubulin by stabilizing microtubuli that are formed. They are able to influence the cell-splitting in a phase-specific manner and are therefore useful in treating diseases or conditions associated with the need for cell growth, division and/or proliferation. Thus the water the same the same the same that the s ovarian, epothilone derivs. are suitable for treating malignant tumors, e.g., ovarian, stomach, colon, adeno-, breast, lung, head and neck carcinomas, malignant melanoma, acute lymphocytic and myelocytic leukemia; and for anti-angiogenesis therapy as well as for treatment of chronic inflammatory diseases (such as psoriasis, arthritis).

303154-56-5P 303154-58-7P 303154-59-8P ΙT 303154-60-1P

> RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 6-alkenyl-, 6-alkynyl- and 6-epoxyepothilone derivs. and their use in pharmaceutical prepns.)

RN303154--56-5 ZCAPLUS

or we are the 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-4)]-10-[(1,1-4)]-10dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-

(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

CN

S 60

SN 10/563058 Page 30 of 69 STIC STN SEARCH RESULTS

L25 ANSWER 10 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2000:790507 ZCAPLUS Full-text

DOCUMENT NUMBER:

133:362656

TITLE:

Preparation of 6-alkenyl-, 6-alkynyl- and

6-epoxyepothilone derivatives and their antitumor

activity

INVENTOR(S):

Klar, Ulrich; Schwede, Wolfgang; Skuballa, Werner; Buchmann, Bernd; Hoffmann, Jens; Lichtner, Rosemarie

PATENT ASSIGNEE(S): Schering Aktiengesellschaft, Germany

SOURCE:

PCT Int. Appl., 298 pp. CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

English

FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

	PATENT NO.					KIND DATE			APPLICATION NO.										
	WO	2000	0665	89				20001109									0000	501	
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			CU,	CZ,	DE,	DK,	DM,	DZ,	EE,	ES,	FI,	GB,	GD,	GE,	GH,	GM,	HR,	HU,	
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SN 10/563058 Page 29 of 69 STIC STN SEARCH RESULTS

PATENT ASSIGNEE(S):

Bristol-Myers Squibb Company, USA

SOURCE:

PCT Int. Appl., 28 pp.

DOCUMENT TYPE:

Patent

CODEN: PIXXD2

LANGUAGE:

English

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

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		W:	ΑE,	AG,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BY,	BZ,	CA,	CH,	CN,
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			HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	ΚP,	KR,	KZ,	LC,	LK,	LR,	LS,
			LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NO,	NZ,	PL,	PT,	RO,
			RU,	SD,	SE,	SG,	SI,	SK,	SL,	ТJ,	TM,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,
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			DE,	DK,	ES,	FI,	FR,	GB,	GR,	IE,	IT,	LU,	MC,	NL,	PT,	SE,	TR,	BF,
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OTHER SOURCE(S):

CASREACT 135:287591; MARPAT 135:287591

The present invention relates to a process for the preparation of intermediates useful in the synthesis of epothilone analogs by initially enzymically degrading certain epothilone compds. to form ring-open structures containing a carboxyl group which is esterified, the hydroxyl groups on the moiety protected and the resulting compound oxidized by, e.g. ozone, to form a first intermediate. The first intermediate can be reacted with a triphenylphosphine adduct to yield a compound containing an ester group at position 1 which is subsequently hydrolyzed to form a second intermediate.

364336-79-8P 364336-83-4P

RL: PUR (Purification or recovery); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation of epothilone intermediates)

RN 364336-79-8 ZCAPLUS

Dodecanoic acid, 3,7-dihydroxy-4,4,6,8-tetramethyl-5,12-dioxo-, methyl CN ester, (3S, 6R, 7S, 8S) - (9CI) (CA INDEX NAME)

Absolute stereochemistry.

364336-83-4 ZCAPLUS RN

Dodecanoic acid, 3,7-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4,6,8-CN tetramethyl-5,12-dioxo-, methyl ester, (3S,6R,7S,8S)- (9CI) (CA INDEX NAME)

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RN 303154-59-8 ZCAPLUS

CN 3-Undecanone, 4-(3-butynyl)-2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-60-1 ZCAPLUS

CN 2,9-Undecanedione, 8-(3-butynyl)-10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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L25 ANSWER 9 OF 25

ZCAPLUS COPYRIGHT 2007 ACS on STN 2001:731069 ZCAPLUS Full-text

ACCESSION NUMBER:

135:287591

TITLE:

Preparation of epothilone intermediates

INVENTOR(S):

Vite, Gregory D.; Kim, Soong-Hoon; Hoeefle, Gerhard

SN 10/563058 Page 27 of 69 STIC STN SEARCH RESULTS

303154-59-8P 303154-60-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of 12,13-cyclopropylepothilone derivs. and their use in pharmaceutical compns.)

RN 303154-56-5 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-57-6 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-58-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

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FILE BEILSTEIN
FILE LAST UPDATED ON September 26, 2007

FILE COVERS 1771 TO 2007.

FILE CONTAINS 10.119,480 SUBSTANCES

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For mo detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

- * PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST.
- * SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE
- * ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE
- * ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS.

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* FOR PRICE INFORMATION SEE HELP COST

NEW

- * PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.
- * NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.

FILE BABS

FILE LAST UPDATED:

FILE COVERS 1980 TO DATE.

25 JUN 2007

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SN 10/563058 Page 26 of 69 STIC STN SEARCH RESULTS

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10041470	A1	20020228	DE 2000-10041470	20000818
PRIORITY APPLN. INFO.:			DE 2000-10041470	20000818
OTHER SOURCE(S):	CASREA	ACT 136:21659	2; MARPAT 136:216592	
GI				

$$X^2 = (CH_2)_m - (CH_2)_p R^{26}$$

The present invention describes new 6-alkenyl- and 6-alkynylepothilone AB derivs., e.g., I [Rla, Rlb = H, C1-10-alkyl, aryl, C7-20-aralkyl; RlaRlb = (CH2)r, CH2OCH2; r = 1 - 5; R2a = H, C1-10-alkyl, aryl, C7-20-aralkyl, (CH2)m-C.tplbond.C-(CH2)pR26, (CH2)m-C:C-(CH2)pR26, X1, X2; n = 0 - 5; p = 0 - 3; m = 00 - 4; R2b = (CH2)m-C.tplbond.C-(CH2)pR26, (CH2)m-C:C- (CH2)pR26, X1, X2; R3a = H, C1-10-alkyl, aryl, C7-20-aralkyl; R3b = O-protecting group; R4 = H, C1-10-alkyl, aryl, C7-20-aralkyl, halogen, OH, O-protecting group, CN; R5 = H, C1-10-alkyl, aryl, C7-20-aralkyl, (CH2)s-T; S=1-4; T=OH, O-protecting-group, halogen; R6R7 = C(R33)2, NR32 AY = OC(:O), OCH2, CH2C(:O), NR29C(:O), -NR29SO2; DE = CH2CH2, CH2O, OCH2; G = X:CR8-, bicyclic or tricyclic aryl; X = O, (O-alkyl)2, etc.; Z = H, H,OH, H,O-protective group; R8 = H, halogen, CN, C1-20-alkyl, aryl, C7-20-aralkyl; R14 = H, OH, halogen, O-SO2-alkyl, O-SO2aryl, O-SO2-aralkyl; R26 = H, C1-10-alkyl, aryl, C7-20-aralkyl, C1-10-acyl, OH, O-protecting group; R29 = H, C1-20-alkyl; R32 = H, C1-4-alkyl, C1-4-acyl; R33 = H, halogen], which interact with tubulins by stabilizing the formed microtubulins (no data). I are able specifically to affect cell division and are suitable, for example for the treatment of malignant tumors ovarial -, stomach -, colon -, adeno -, chest -, lungs -, head and neck carcinoma, malignant melanoma, acute lymphocytic and myelocytic leukemia. In addition I are suitable for the anti-angiogenesis therapy as well as for the treatment of chronic ignitable illnesses (psoriasis, arthritis). For the avoidance of uncontrolled cell rampant growths on as well as the better compatibility of medical implants I can be up and/or brought into polymers materials. According to invention, I can be used alone or for the achievement of additive or synergistic effects in combination with further principles and substance classes applicable in the tumor therapy. Exptl. data from patents PCT/EP00/01333 and PCT/IB00/00657 are reproduced here. IT

303154-56-5P 303154-57-6P 303154-58-7P

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Ι

AB A facile and efficient route to epothilone analogs has been developed from the natural product epothilone D (I). Degradation of I via an oxidative cleavage sequence provides acid intermediate II rapidly in six steps. From II, a variety of epothilone analogs have been prepared utilizing ring-closing metathesis to reconstruct the trisubstituted-12,13-double bond. Using this approach, we report a number of epothilone analogs with varying C-15 aromatic side chains and C-14 allylic substitutions and their antitumor activities.

IT 681259-79-0P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation of epothilone D analogs via semisynthetic degradation and ring-closing metathesis and their antitumor activity)

RN 681259-79-0 ZCAPLUS

CN Tridecanoic acid, 3,7-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4,6,8-tetramethyl-5,12-dioxo-, methyl ester, (3S,6R,7S,8S)- (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 8 OF 25 ACCESSION NUMBER:

CAPLUS COPYRIGHT 2007 ACS on STN 2002:157050 ZCAPLUS Full-text

DOCUMENT NUMBER:

136:216592

14

TITLE:

Procedures for the production of 12,13-

cyclopropylepothilone derivatives, as well as for

their use in pharmaceutical preparations

PATENT ASSIGNEE(S):

SOURCE:

Schering Ag, Germany

Ger. Offen., 64 pp.

CODEN: GWXXBX

DOCUMENT TYPE:

Patent German

LANGUAGE:

m. 1

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

SN 10/563058 Page 24 of 69 STIC STN SEARCH RESULTS

RN 823203-24-3 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,4,6-trimethyl-, (4S,5R,6S)-(CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 7 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2004:106102 ZCAPLUS Full-text

ACCESSION NUMBER:
DOCUMENT NUMBER:

140:357084

TITLE:

Rapid access to epothilone analogs via semisynthetic

degradation and reconstruction of epothilone D

AUTHOR(S):

Dong, Steven D.; Sundermann, Kurt; Smith, Karen M. J.;

Petryka, Joseph; Liu, Fenghua; Myles, David C.

CORPORATE SOURCE:

Department of Chemistry, Kosan Biosciences, Hayward,

CA, 94545, USA

SOURCE:

Tetrahedron Letters (2004), 45(9), 1945-1947

CODEN: TELEAY; ISSN: 0040-4039

PUBLISHER:

Elsevier Science B.V.

DOCUMENT TYPE:

Journal

LANGUAGE:

English

OTHER SOURCE(S):

CASREACT 140:357084

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RN 823203-04-9 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(2-propenyl)-, (4R,5S,6S,10R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 823203-05-0 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(2-propenyl)-, (4R,5S,6S,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 823203-23-2 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,4,6-trimethyl-, (4R,5S,6S)-(CA INDEX NAME)

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RN 220774-59-4 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(phenylmethyl)-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-56-5 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-57-6 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-[4-(trimethylsilyl)-3-butynyl]-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

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823203-04-9P 823203-05-0P 823203-23-2P 823203-24-3P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and tetrahydropyranylation of; method for producing C1-C15 fragments of epothilones and derivs. thereof)
RN 220774-19-6 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-20-9 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-4-ethyl-5-hydroxy-2,6-dimethyl-,

Absolute stereochemistry.

(4S, 5R, 6S) - (9CI) (CA INDEX NAME)

RN 220774-58-3 ZCAPLUS
CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-hydroxy-2,6-dimethyl-4-(phenylmethyl)-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

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IT 823203-07-2P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and perruthenate oxidation of; method for producing C1-C15 fragments of epothilones and derivs. thereof)

RN 823203-07-2 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-4-(2-propenyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 823203-19-6P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and silylation of; method for producing C1-C15 fragments of epothilones and derivs. thereof)

RN 823203-19-6 ZCAPLUS

CN 2,9-Tridecanedione, 7,11,13-trihydroxy-6,10,10-trimethyl-8-(2-propenyl)-, (6S,7S,8R,11S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 220774-19-6P 220774-20-9P 220774-58-3P 220774-59-4P 303154-56-5P 303154-57-6P

SN 10/563058 Page 19 of 69 STIC STN SEARCH RESULTS

preparation); PREP (Preparation); RACT (Reactant or reagent)
 (preparation and detetrahydropyranylation of; method for producing C1-C15
 fragments of epothilones and derivs. thereof)

RN 823203-17-4 ZCAPLUS

CN 3-Nonanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-5-hydroxy-2,6-dimethyl-9-(2-methyl-1,3-dioxolan-2-yl)-4-(2-propenyl)-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 823203-18-5 ZCAPLUS

CN 3-Nonanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-5-hydroxy-2,6-dimethyl-9-(2-methyl-1,3-dioxolan-2-yl)-4-(2-propenyl)-, (4S,5R,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 220774-23-2P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and detrahydropyranylation/deketalization of; method for producing C1-C15 fragments of epothilones and derivs. thereof)

-- 1 2

RN 220774-23-2 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-8-ethyl-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA'INDEX NAME)

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RN 823203-06-1 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-4-(2-propenyl)-5[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 823203-25-4 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,4,6-trimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (CA INDEX NAME)

Absolute stereochemistry:

IT 823203-17-4P 823203-18-5P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic

SN 10/563058 Page 17 of 69 STIC STN SEARCH RESULTS

IT 220774-21-0P 220774-60-7P 303154-58-7P 823203-06-1P 823203-25-4P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and desilylation of; method for producing C1-C15 fragments of epothilones and derivs. thereof)

RN 220774-21-0 ZCAPLUS

Absolute stereochemistry.

RN 220774-60-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-4-(phenylmethyl)-5[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-58-7 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-4-[4-(trimethylsilyl)-3-butynyl]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

SN 10/563058 Page 16 of 69 STIC STN SEARCH RESULTS

trimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (CA INDEX NAME)

Absolute stereochemistry.

IT 823203-08-3P 823203-20-9P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(preparation and Wittig reaction of, with (benzothiazolylpropyl)phosphonium iodide derivative; method for producing C1-C15 fragments of epothilones and derivs. thereof)

RN 823203-08-3 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-8-(2-propenyl)-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 823203-20-9 ZCAPLUS

CN 2,9-Tridecanedione, 7,11,13-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6,10,10-trimethyl-8-(2-propenyl)-, (6S,7S,8R,11S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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SN 10/563058 Page 15 of 69 STIC STN SEARCH RESULTS

RN 220774-22-1 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-4-ethyl-10-hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 220774-61-8 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,6-dimethyl-4-(phenylmethyl)-5-[(tetrahydro-2H-pyran-2-yl)oxy]-, (4R,5S,65) (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-59-8 ZCAPLUS

CN 3-Undecanone, 4-(3-butynyl)-2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10hydroxy-2,6-dimethyl-5-[(tetrahydro-2H-pyran-2-yl).oxy]-, (4R,5S,6S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 823203-27-6 ZCAPLUS

CN 3-Undecanone, 2-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-10-hydroxy-2,4,6-

SN 10/563058 Page 14 of 69 STIC STN SEARCH RESULTS

RN 220775-76-8 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,8,10-trimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 303154-60-1 ZCAPLUS

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2,9-Undecanedione, 8-(3-butynyl)-10-[(4S)-2,2-dimethyl-1,3-dioxan+4-yl]-6,10-dimethyl-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 823203-02-7 ZCAPLUS

CN 2,9-Tridecanedione, 8-ethyl-7,11,13-trihydroxy-6,10,10-trimethyl-, (6S,7S,8R,11S)- (CA INDEX NAME)

Absolute stereochemistry.

IT 220774-22-1P 220774-61-8P 303154-59-8P 823203-27-6P

RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation and Swern oxidation of; method for producing C1-C15 fragments

epothilones and derivs. thereof)

SN 10/563058 Page 13 of 69 STIC STN SEARCH RESULTS

alkyl, aryl, C7-20-aralkyl; R6, R7 = H; R6R7 = bond, O; G = X:CR8, bi- or tricyclic aryl; R8 = H, halogen, (un) substituted C1-20-alkyl, aryl, C7-20aralkyl; X = O, (OR23)2, C2-10-alkylene- α , ω -dioxy, H(OR9), CR10R11; R23 = C1-20-alkyl; R9 = H, protecting group; R10, R11 = H, C1-10-alkyl, aryl, C7-20aralkyl; CR10R11 = 5 - to 7-membered carbocycle; R13 = CH2OR13a, CH2-halo, CHO, CO2R13b, CO-halo; R13a, R14a = H, SO2alkyl, SO2-aryl, SO2-aralkyl; R13aR14a = (CH2)o, CR15aR15b; o = 2 - 4; R13b, R14b = H, C1-10-alkyl, aryl,C7-20-aralkyl; R15a, R15b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R15aR15b = (CH2)q; q = 3 - 6; R20 = O-PG, NHR29, N3; Z = O, H(OR12); R12 = H, PG] ofepothilones and derivs. The procedure comprises the bonding of a C1-C6 - Avfragment, R13CH2CHR14CR1aR1bC(:O)CHR2aR2b, to a C7-C12 fragment, R5C(:V)(CH2)3CR4aR4bC(:W)R3a [V, W = O, (OR23)2, C2-10-alkylene- α , ω -dioxy, H(OR9)], to form a C1-C12 fragment, R5C(:V)(CH2)3CR4aR4bCR3a(O-PG14)CR2aR2bC(:Z)CR1aR1bCHR14CH2R13 [PG = H, protecting group], which is then treated with a C13-C15 fragment, G-CR20'CH2CHR7'R21 [R7' = H; R20' = halogen, N3, NHR29, OH, O-PG, NR29-PG, C1-20-(perfluoro)alkylsulfonyloxy, (C1-4-alkyl, NO2, Cl, Br-substituted) benzyloxy, NR29SO2Me, NR29C(:O)Me, CH2C(:O)Me; R21 = OH, halo, O-PG, P+Ph3Hal- (Hal = F, Cl, Br, I), P(O)(OQ)2 (Q = C1-10-alkyl, Ph), P(:0) Ph2; R29 = H, C1-6-alkyl], to form the C1-C15 epothilone intermediate product I. Thus, I [R1a = R1b = R5 = Me, R2a = CH2CH: CH2- β , R2b $R4b = H-\alpha$, $R3 = H-\beta$, $R4a = Me-\beta$, R6R7 = bond, R13 = CO2H, R14 = OSiMe2CMe35cSi β , R20 = OSiMe2CMe3- α , G = 2-methylbenzothiazol-5- yl, PG = SiMe2CMe3, Z = O] was prepared from (S)-4-(2-methyl-3-oxohept-6-en-2-yl)-2,2-dimethyl-1,3dioxane via lithiation and reaction with (2S,6RS)-2-methyl-6-[(tertbutyldimethylsilyl)oxy]heptanal, tetrahydropyranylation, desilylation with Bu4NF in THF, oxidation in CH2Cl2 containing N-methylmorpholine N-oxide and catalytic tetrapropylammonium perruthenate, Wittig reaction with [(3S)-3-(2methylbenzothiazol-5- yl)propyl]triphenylphosphonium iodide, deisopropylidenation/detetrahydropy ranylation with catalytic 4-MeC6H4SO3H in EtOH, silylation with CF3SO2SiMe2CMe3, regioselective desilylation with (\pm) camphor-10- sulfonic acid, Swern oxidation with DMSO/(COC1)2 in CH2C12 and carbonyl oxidation with NaOCl2 in aqueous THF/Me3COH. The produced C1-C15 epothilone intermediate products can be converted into the intrinsically active ingredients II [AK = OC(:0), OCH2, CH2C(:0), NR29C(:0), NR29SO2; R29 = H, C1-6-alkyl] according to known methods. The invention also relates to the corresponding C1-C12 fragments.

IT 220774-62-9P 220775-76-8P 303154-60-1P 823203-02-7P

RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)

(method for producing C1-C15 fragments of epothilones and derivs. thereof)

RN 220774-62-9 ZCAPLUS

CN 2,9-Undecanedione, 10-[(4S)-2,2-dimethyl-1,3-dioxan-4-yl]-6,10-dimethyl-8-(phenylmethyl)-7-[(tetrahydro-2H-pyran-2-yl)oxy]-, (6S,7S,8R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

SN 10/563058 Page 12 of 69 STIC STN SEARCH RESULTS

Skuballa, Werner

PATENT ASSIGNEE(S):

Schering Aktiengesellschaft, Germany

SOURCE:

PCT Int. Appl., 48 pp.

CODEN: PIXXD2

DOCUMENT TYPE:

Patent

LANGUAGE:

German

FAMILY ACC. NUM. COUNT:

PATENT INFORMATION:

DATE PATENT NO. KIND APPLICATION NO. DATE _____ WO 2005003071 **A**1 20050113 WO 2004-EP6685 20040619 AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK; LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, A SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG DE 10331004 **A1** 20050224 DE 2003-10331004 20030703 AU 2004254200 **A**1 20050113 AU 2004-254200 20040619 CA 2531078 **A**1 20050113 CA 2004-2531078 20040619 EP 1641734 A1 20060405 EP 2004-740122 20040619 AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR 20060809 CN 2004-80019005 CN 1816514 Α 20040619 BR 2004012179 Α 20060822 BR 2004-12179 20040619 IN 2006DN00056 Α 20070824 IN 2006-DN56 20060103 MX 2006PA00172 20060427 MX 2006-PA172 Α 20060105 NO 2006000554 Α 20060403 NO 2006-554 20060202 US 2006-563058 US 2007142675 A1 20070621 20060619 PRIORITY APPLN. INFO.: DE 2003-10331004 Α 20030703 WO 2004-EP6685 W 20040619 OTHER SOURCE(S): CASREACT 142:113814; MARPAT 142:113814

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GI

R6 R5
R7
R4?
R3
OPG
R1? R4?
R2?

II

AB The invention relates to a method for preparing C1-C15 fragments I [R1a, R1b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R1aR1b = (CH2)m; m = 2 - 5; R2a, R2b = H, C1-10-alkyl, C2-10-alkenyl, C2-10-alkynyl, aryl, C7-20-aralkyl; R2aR2b = (CH2)n; n = 2 - 5; R3 = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4a, R4b = H, C1-10-alkyl, aryl, C7-20-aralkyl; R4aR4b = (CH2)p; p = 2 - 5; R5 = H, C1-10-

SN 10/563058 Page 11 of 69 STIC STN SEARCH RESULTS

AB Synthesis of C1-C12 segment of epothilones A and B was achieved via diastereo-and regioselective opening of a trisubstituted epoxy ketone at the more substituted carbon. Epoxide I (R = SiMe2CMe3, R1 = benzyl) was cleaved selectively at the more substituted carbon using SmI2 in MeOH/THF at -90° to form the silyl protected β -hydroxyketone II which contains the C5-C7 epothilone aldol moiety.

IT 201683-59-2P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(synthesis of C1-C12 segment of epothilones A and B via radical induced opening of trisubstituted epoxides)

RN 201683-59-2 ZCAPLUS

CN Dodecanoic acid, 7-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-hydroxy-4,4,6,8-tetramethyl-5-oxo-12-(phenylmethoxy)-, 1,1-dimethylethyl ester, [3S-(3R*,6S*,7R*,8R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 201683-49-0P

RL: SPN (Synthetic preparation); PREP (Preparation)

(synthesis of C1-C12 segment of epothilones A and B via radical induced opening of trisubstituted epoxides)

RN 201683-49-0 ZCAPLUS

CN Dodecanoic acid, 3,7-bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4,4,6,8-tetramethyl-5-oxo-12-(phenylmethoxy)-, 1,1-dimethylethyl ester, [3S-(3R*,6S*,7R*,8R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS

L25 ANSWER 6 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:

2005:29293 ZCAPLUS Full-text

DOCUMENT NUMBER:

142:113814

TITLE:

10 E

Method for producing C1-C15 fragments of epothilones

and derivatives thereof

INVENTOR(S):

Klar, Ulrich; Buchmann, Bernd; Schwede, Wolfgang;

SN 10/563058 Page 10 of 69 STIC STN SEARCH RESULTS

RN 346652-91-3 ZCAPLUS

CN Dodecanal, 6,10,12-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,7,9,9-tetramethyl-8-oxo-, (5S,6S,7R,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

117 THERE ARE 117 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L25 ANSWER 5 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 5

ACCESSION NUMBER:

1998:14400 ZCAPLUS Full-text

DOCUMENT NUMBER:

128:114806

TITLE:

Radical-induced opening of trisubstituted epoxides: application in the synthesis of C1-C12 segment of

epothilones

AUTHOR(S):

Chakraborty, T. K.; Dutta, S.

CORPORATE SOURCE:

Indian Inst. Chem. Technol., Hyderabad, 500 007, India

SOURCE: Tetrahe

Tetrahedron Letters (1998), 39(1/2), 101-104

CODEN: TELEAY; ISSN: 0040-4039

PUBLISHER:

Elsevier Science Ltd.

DOCUMENT TYPE:

Journal

LANGUAGE:

English

OTHER SOURCE(S):

CASREACT 128:114806

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SN 10/563058 Page 9 of 69 STIC STN SEARCH RESULTS

AB Naturally occurring epothilones have been synthesized starting from enantiomerically pure aldol compds. I and II, which were obtained by antibody catalysis. Aldolase antibody 38C2 catalyzed the resolution of (±)-I by enantioselective retro-aldol reaction to afford I in 90% ee at 50% conversion. Compds. II (R = Me, CH2OH) were obtained in more than 99% ee at 50% conversion by resolution of their racemic mixts. using newly developed aldolase antibodies 84G3, 85H6 or 93F3. Compds. I and II were resolved in multigram quantities and then converted to the epothilones by metathesis processes, which were catalyzed by Grubbs' catalysts.

IT 346651-96-5P

RL: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of epothilones A-F)

RN 346651-96-5 ZCAPLUS

CN 2,9-Tridecanedione, 7,11,13-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6,8,10,10-tetramethyl-, (6S,7S,8R,11S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

IT 346652-88-8P 346652-91-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of epothilones A-F)

RN 346652-88-8 ZCAPLUS

CN 4,12-Dioxa-3,13-disilapentadecan-7-one, 9-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5-[(1S)-5-hydroxy-1-methylpentyl]-2,2,3,3,6,8,8,13,13,14,14-undecamethyl=a,(5S,6R,9S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

SN 10/563058 Page 8 of 69 STIC STN SEARCH RESULTS

CORPORATE SOURCE:

Abteilung Naturstoffchemie, Gesellschaft fuer Biotechnologische Forschung mbH, Braunschweig,

D-38124, Germany

SOURCE:

Journal of the Chemical Society, Perkin Transactions 1

(2002), (22), 2490-2503

CODEN: JCSPCE; ISSN: 1472-7781 Royal Society of Chemistry

PUBLISHER: DOCUMENT TYPE:

Journal

LANGUAGE:

English

OTHER SOURCE(S):

CASREACT 138:187542

and a AB. AB. Novel and unique chiral building blocks of high structural diversity were a second of obtained by selective chemical fragmentation of natural products from myxobacteria. Subsequent modification reactions provided primary alc. and carboxylic acid derivs., which are suitable for the construction of combinatorial chemical libraries. The single SPOT synthesis of a hybrid structure on a polypropylene membrane was employed to demonstrate the chemical recombination of such rare building blocks on a micro-scale.

IT498580-02-2P

> RL: SPN (Synthetic preparation); PREP (Preparation) (fragmentation of natural products from myxobacteria as building blocks for combinatorial synthesis)

498580-02-2 ZCAPLUS

Dodecanoic acid, 3,7,12-trihydroxy-4,4,6,8-tetramethyl-5-oxo-, methyl ester, (3S, 6R, 7S, 8S) - (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 4 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 4

ACCESSION NUMBER:

2001:316603 ZCAPLUS Full-text

DOCUMENT NUMBER:

135:76707

50

TITLE:

Catalytic antibody route to the naturally occurring

AUTHOR(S):

epothilones: total synthesis of epothilones A - F Sinha, Subhash C.; Sun, Jian; Miller, Gregory P.;

Wartmann, Markus; Lerner, Richard A.

CORPORATE SOURCE:

Department of Molecular Biology and the Skaggs

Institute for Chemical Biology, The Scripps Research

Institute, La Jolla, CA, 92037, USA

SOURCE:

Chemistry--A European Journal (2001), 7(8), 1691-1702

CODEN: CEUJED; ISSN: 0947-6539

PUBLISHER:

Wiley-VCH Verlag GmbH

DOCUMENT TYPE:

LANGUAGE:

Journal English

OTHER SOURCE(S):

CASREACT 135:76707

GT

SN 10/563058 Page 7 of 69 STIC STN SEARCH RESULTS

English

CODEN: ACIEF5; ISSN: 1433-7851

Wiley-VCH Verlag GmbH & Co. KGaA

DOCUMENT TYPE:

PUBLISHER:

Journal

LANGUAGE: OTHER SOURCE(S):

CASREACT 139:197285

GI

AB A total synthesis of epothilone C (I) with concomitant formal synthesis of epothilone A is described, using immobilized reagents and scavengers to effect multistep synthetic transformations and purifications.

IT 346652-91-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of epothilones using solid-supported reagents and scavengers)

RN 346652-91-3 ZCAPLUS

CN Dodecanal, 6,10,12-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,7,9,9-tetramethyl-8-oxo-, (5S,6S,7R,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

73 THERE ARE 73 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L25 ANSWER 3 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 3

ACCESSION NUMBER:

2002:863402 ZCAPLUS Full-text

DOCUMENT NUMBER:

138:187542

TITLE:

Natural product-derived building blocks for

combinatorial synthesis. Part 1. Fragmentation of

natural products from myxobacteria

AUTHOR(S):

Niggemann, Jutta; Michaelis, Katrin; Frank, Ronald;

Zander, Norbert; Hoefle, Gerhard

12 14 3

SN 10/563058 Page 6 of 69 STIC STN SEARCH RESULTS

AB The total synthesis of the cytotoxic antitumor natural product epothilone C has provided a stage for the exploitation and further development of immobilized reagent methods. A stereoselective convergent synthetic strategy was applied, incorporating polymer-supported reagents, catalysts, scavengers and catch-and-release techniques to avoid frequent aqueous work-up and chromatog. purification The enantioselective preparation of 3 key fragments heptanone I, (S)-2-methyl-6-heptenal, and thiazole II along with their elaboration via diastereoselective coupling into epothilone C is presented.

IT 346652-91-3P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(total synthesis of epothilone C via asym. synthesis and stereoselective coupling of heptanone, methylheptenal, and thiazole fragments using immobilized reagents and scavengers)

RN 346652-91-3 ZCAPLUS

CN Dodecanal, 6,10,12-tris[[(1,1-dimethylethyl)dimethylsilyl]oxy]-5,7,9,9-tetramethyl-8-oxo-, (5S,6S,7R,10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

122 THERE ARE 122 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE REFORMAT

L25 ANSWER 2 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 2

ACCESSION NUMBER:

2003:494861 ZCAPLUS Full-text

DOCUMENT NUMBER:

139:197285

TITLE:

A total synthesis of epothilones using solid-supported

reagents and scavengers

AUTHOR(S):

Storer, R. Ian; Takemoto, Toshiyasu; Jackson, Philip

S.; Ley, Steven V.

CORPORATE SOURCE:

University Chemical Laboratories, University of

Cambridge, Cambridge, CB2 1EW, UK

SOURCE:

Angewandte Chemie, International Edition (2003),

42(22), 2521-2525

SN 10/563058 Page 5 of 69 STIC STN SEARCH RESULTS

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25 JUN 2007

·<20070625/UP>

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L14

7 SEA FILE=BABS ABB=ON PLU=ON (6300090/BABSAN OR 6630563/BABSAN OR 6085475/BABSAN OR 6376421/BABSAN OR 6410256/BABSAN OR 6473119/BABSAN OR 6597156/BABSAN)

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PROCESSING COMPLETED FOR L19 PROCESSING COMPLETED FOR L14

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25 DUP REM L6 L19 L14 (7 DUPLICATES REMOVED)

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L25 ANSWER 1 OF 25 ZCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 1

ACCESSION NUMBER:

2004:454851 ZCAPLUS Full-text

DOCUMENT NUMBER:

141:140221

TITLE:

Multi-step application of immobilized reagents and

scavengers: A total synthesis of epothilone C

AUTHOR(S):

Storer, R. Ian; Takemoto, Toshiyasu; Jackson, Philip

S.; Brown, Dearg S.; Baxendale, Ian R.; Ley, Steven V.

CORPORATE SOURCE:

Department of Chemistry, University of Cambridge,

Cambridge, CB2 1EW, UK

SOURCE:

Chemistry--A European Journal (2004), 10(10),

2529-2547

CODEN: CEUJED; ISSN: 0947-6539

PUBLISHER:

Wiley-VCH Verlag GmbH & Co. KGaA

DOCUMENT TYPE:

Journal English

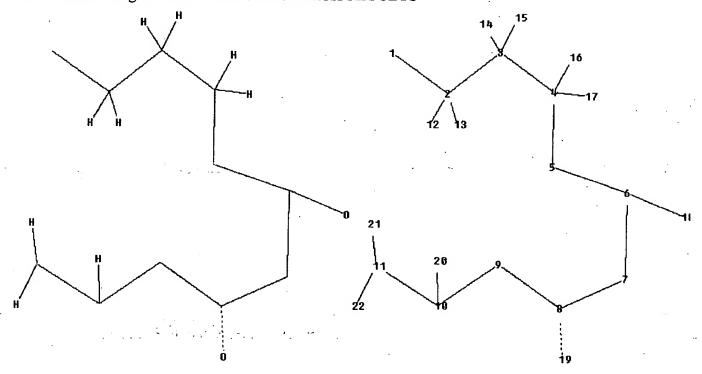
LANGUAGE: OTHER SOURCE(S):

CASREACT 141:140221

CT

ing were the

SN 10/563058 Page 4 of 69 STIC STN SEARCH RESULTS



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ring/chain nodes:
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chain bonds:
2-12 2-13 3-14 3-15 4-16 4-17 6-18 8-19 10-20 11-21 11-22
ring/chain bonds:
1-2 2-3 3-4 4-5 5-6 6-7 7-8 8-9 9-10 10-11
exact/norm bonds:
1-2 2-3 3-4 4-5 5-6 6-7 6-18 7-8 8-9 8-19 9-10 10-11
exact bonds:
2-12 2-13 3-14 3-15 4-16 4-17 10-20 11-21 11-22
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Match level:

1:GLASS 2:CLASS 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLASS 10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS 19:CLASS 20:CLASS 21:CLASS 22:CLASS

L3		SCR	1008			
L11	38	SEA	FILE=BEILSTEIN	SSS FUL	L1 AND	L3
L12	26	SEA	FILE=BEILSTEIN	ABB=ON	PLU=ON	L11/COM
L13	- 5	SEA	FILE=BEILSTEIN	ABB=ON	PLU=ON	L12 AND BABSAN/FA
L15			FILE=BEILSTEIN			L12 NOT L13
L16	14	SEA	FILE=BEILSTEIN	ABB=ON	PLU=ON	L15 AND RN/FA
L19	7	SEA	FILE=BEILSTEIN	ABB=ON	PLU=ON	1.15 NOT 1.16

=> file babs

FILE 'BABS' ENTERED AT 15:47:02 ON 11 OCT 2007 COPYRIGHT (c) 2007 Beilstein-Institut zur Foerderung der Chemischen Wissenschaften

SN 10/563058 Page 3 of 69 STIC STN SEARCH RESULTS

FILE COVERS 1771 TO 2007.

*** FILE CONTAINS 10.119,480 SUBSTANCES ***

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For mo detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

*********************** * PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST. * SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE * ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE * ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS. * FOR PRICE INFORMATION SEE HELP COST

NEW

- * PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.
- * NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES; ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.

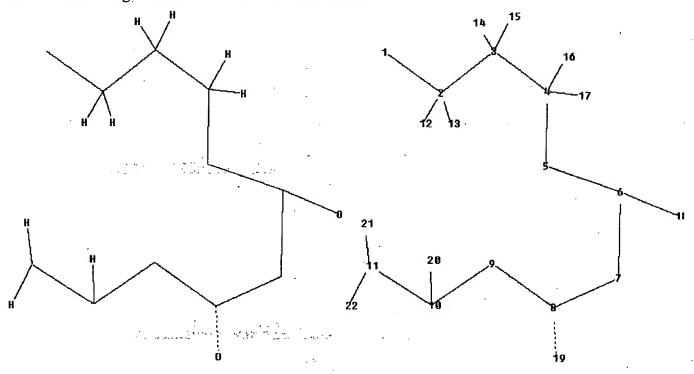
=> d stat que L19 L1

1 1000

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation: Uploading L1.str

SN 10/563058 Page 2 of 69 STIC STN SEARCH RESULTS



chain nodes:
12 13 14 15 16 17 18 19 20 21 22
ring/chain nodes:
1 2 3 4 5 6 7 8 9 10 11
chain bonds:
2-12 2-13 3-14 3-15 4-16 4-17 6-18 8-19 10-20 11-21 11-22
ring/chain bonds:
1-2 2-3 3-4 4-5 5-6 6-7 7-8 8-9 9-10 10-11
exact/norm bonds:
1-2 2-3 3-4 4-5 5-6 6-7 6-18 7-8 8-9 8-19 9-10 10-11
exact bonds:
2-12 2-13 3-14 3-15 4-16 4-17 10-20 11-21 11-22

Match level :

1:CLASS 2:CLASS 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLASS 10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS 19:CLASS 22:CLASS 21:CLASS 22:CLASS

L3 SCR 1008 L5 68 SEA FILE=REGISTRY SSS FUL L1 AND L3 L6 18 SEA FILE=ZCAPLUS ABB=ON PLU=ON L5

=> file beilstein

FILE 'BEILSTEIN' ENTERED AT 15:46:51 ON 11 OCT 2007 COPYRIGHT (c) 2007 Beilstein-Institut zur Foerderung der Chemischen Wissenschaften licensed to Beilstein GmbH and MDL Information Systems GmbH

FILE LAST UPDATED ON September 26, 2007

SN 10/563058 Page 1 of 69 STIC STN SEARCH RESULTS

=> file registry
FILE 'REGISTRY' ENTERED AT 15:46:28 ON 11 OCT 2007
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 10 OCT 2007 HIGHEST RN 950149-06-1 DICTIONARY FILE UPDATES: 10 OCT 2007 HIGHEST RN 950149-06-1

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH June 29, 2007

Please note that search-term pricing does apply when conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> file zcaplus

FILE 'ZCAPLUS' ENTERED AT 15:46:31 ON 11 OCT 2007

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FILE COVERS 1907 - 11 Oct 2007 VOL 147 ISS 16 FILE LAST UPDATED: 10 Oct 2007 (20071010/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

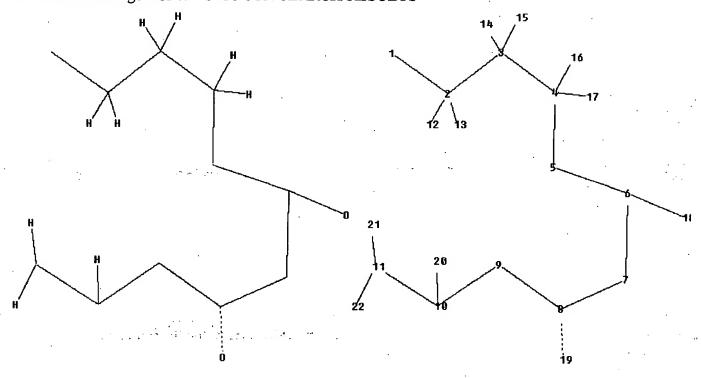
This file contains CAS Registry Numbers for easy and accurate substance identification.
'OBI' IS DEFAULT SEARCH FIELD FOR 'ZCAPLUS' FILE

=> d stat que L6 L1 STR

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation: Uploading L1.str

SN 10/563058 Page 4 of 69 STIC STN SEARCH RESULTS



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chain nodes :
12  13  14  15  16  17  18  19  20  21  22
ring/chain nodes :
1  2  3  4  5  6  7  8  9  10  11
chain bonds :
2-12  2-13  3-14  3-15  4-16  4-17  6-18  8-19  10-20  11-21  11-22
ring/chain bonds :
1-2  2-3  3-4  4-5  5-6  6-7  7-8  8-9  9-10  10-11
exact/norm bonds :
1-2  2-3  3-4  4-5  5-6  6-7  6-18  7-8  8-9  8-19  9-10  10-11
exact bonds :
2-12  2-13  3-14  3-15  4-16  4-17  10-20  11-21  11-22
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Match level:

1:CLASS 2:CLASS 3:CLASS 4:CLASS 5:CLASS 6:CLASS 7:CLASS 8:CLASS 9:CLASS 10:CLASS 11:CLASS 12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS 19:CLASS 20:CLASS 21:CLASS 22:CLASS

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L3
               SCR 1008
L11
            38 SEA FILE=BEILSTEIN SSS FUL L1 AND L3
L12
            26 SEA FILE=BEILSTEIN ABB=ON PLU=ON L11/COM
            5 SEA FILE=BEILSTEIN ABB=ON PLU=ON L12 AND BABSAN/FA
L13
L15
          21 SEA FILE=BEILSTEIN ABB=ON PLU=ON L12 NOT L13
L16
            14 SEA FILE=BEILSTEIN ABB=ON
                                         PLU=ON L15 AND RN/FA
L19
             7 SEA FILE=BEILSTEIN ABB=ON
                                         PLU=ON L15 NOT L16
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=> file babs

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SN 10/563058 Page 3 of 69 STIC STN SEARCH RESULTS

FILE COVERS 1771 TO 2007.

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>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For mo detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE : <<<

- NEI
- * PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.
- * NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

Structure attributes must be viewed using STN Express query preparation: Uploading L1.str

Intern al Application No

			1721 2004/ 000000	
IPC 7	SIFICATION OF SUBJECT MATTER C07C49/17 C07D417/06 C07D	193/04	-	
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	lo International Patent Classification (IPC) or to both national ch	ssification and IPC		
	S SEARCHED			
IPC 7	tocumentation searched (classification system tollowed by class CO7C CO7D ,	(fication symbols)		
Documenta	allon searched other than minimum documentation to the extent	that such documents are included i	in the fields searched	
	· -		, and lower sequency	
	data base consulted during the International search (name of da		th terms used)	
EPO-In	ternal, PAJ, BEILSTEIN Data, CHEM	ABS Data	•	
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT	·		
Category *	Citation of document, with indication, where appropriate, of th	e relevant passages	Relevant to claim No.	
			TODADII (O CIAINI NO.	
X	WO 99/07692 A (KLAR ULRICH ; SO (DE); BUCHMANN BERND (DE); SKUI	BALLA WERNER	1-5	
	() 18 February 1999 (1999-02-19 cited in the application	•		
	page 49, line 1 - page 50, line	e 15; claim	·	
	US 2003/0144	1522		
- 1				
Furthe	r documents are listed in the continuation of box C.	X Patent family members	are listed in annex.	
	gories of cited documents :	T later document published aff	er the international films date	
consider	I defining the general state of the art which is not ed to be of particular relevance		onflict with the application but to theory underlying the	
filing date "X" document of particular relevance; the claimed invention cannot be considered noted or cannot be considered to				
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•	NL - 2280 HV R∯swijk Tel (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seelmann, I		
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Abstract

This invention describes a process for the production of C₁-C₁₅-fragments of epothilones and derivatives thereof, in which a C1-C6-fragment is linked with a C7-C12-fragment to a C1-C12-fragment, and the latter then is reacted with a C13-C15-fragment to form the C1-C15 initial epothilone product that is to be produced.

The thus obtained C1-C15 initial epothilone products can be reacted according to known methods to form the actual active ingredients.

In addition, the invention relates to the corresponding C1-C12-fragments.

PATENT COOPERATION TREAT

PCT

10/563058 LSR

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Telephone No.

Facsimile No.

Translation

International application No.
PCT/EP2004/006685

Box	No. I Basis of the report	
1.	With regard to the language, this report is based on the internation	nal application in the language in which it was filed, unless otherwise
	This report is based on translations from the original language which is the language of a translation furnished for the purp	ge into the following language
	international search (Rule 12.3 and 23.1(b))	
	publication of the international application (Rule 12.4)
	international preliminary examination (Rule 55.2 and	
2.	receiving Office in response to an invitation under Article 14 at this report):	report is based on (replacement sheets which have been furnished to the re referred to in this report as "originally filed" and are not annexed to
	the international application as originally filed/furnished	
	the description:	as animally filed/franished
		as originally filed/furnished
		received by this Authority on
ŀ		received by this Authority on
	the claims:	
ļ	nos. 1-5	as originally filed/furnished
	nos.*	as amended (together with any statement) under Article 19
	nos.*	received by this Authority on
	nos.*	received by this Authority on
	the drawings:	
	sheets	as originally filed/furnished
	sheets*	received by this Authority on
	sheets*	received by this Authority on
	a sequence listing and/or any related table(s) - see Suppler	mental Box Relating to Sequence Listing.
3.	The amendments have resulted in the cancellation of:	
].	the description, pages	
	the claims, nos.	
	the drawings, sheets/figs	
	any table(s) related to sequence listing (specify):	Just account to this report and listed below had not been made since
4.	they have been considered to go beyond the disclosure as	
	the description, pages	
	the claims, nos.	
	the drawings, sheets/figs	
	the sequence listing (specify):	
	any table(s) related to sequence listing (specify):	
Ŀ	If item 4 applies, some or all of those sheets may be marked "sa	perseded."

International application No.
PCT/EP2004/006685

Box		Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement				
1.	Statement		·			
	Novelty (N)	Claims		_ YES		
		Claims	1-5	_ мо		
	Inventive step (IS)	Claims		YES		
		Claims	1-5	_ NO		
	Industrial applicability (IA)	Claims	1-5	_ YES		
		Claims	, , , , , , , , , , , , , , , , , , ,	_ NO		

2. Citations and explanations (Rule 70.7)

The present application appears not to satisfy the requirements of PCT Article 33(2) because the subject matter of the claims is not novel. Claim 9 and pages 49-50 of the description of document D1 (WO 99/07692 A) concern, inter alia, a method for producing epothilone derivatives from the fragments A+B = A-B and A-B + C = A-B-C, wherein all three fragments structurally overlap the A, B and C claimed in the present application. The formula AB in claim 9 of document D1 therefore appears to be prejudicial to the novelty of the present claim 5. The method of claim 9 of document D1 likewise appears to be prejudicial to the novelty of present claims 1-4. In particular, in the C fragment U=C-R appears to overlap with G in document D1, and in fragment AB CH-CH versus D-E in AB of document D1 does not result in a new selection, since D-E form a unit, that is to say, they cannot be selected independently of each other. Consequently, this is considered no more than a selection from a list.

Document D1 is the closest prior art. It discloses the production of epothilone derivatives from the fragments A+B=A-B and A-B+C=A-B-C. The problem to be solved

International application No.
PCT/EP2004/006685

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

by the present invention is understood to be that of providing an alternative method for producing epothilones. In the light of the experimental part it can be assumed that this problem is solved by the application. However, insofar as the subject matter of the present application can be considered novel, the fragments A, B and C are similar to those of document D1 to such an extent that the solution is obvious to a person skilled in the art. The problem to be solved by the present application must therefore be considered that of an alternative method having unexpected or surprising properties with respect to the closest prior art (D1). Without comparative test results or other arguments demonstrating the patentability of the invention it is not possible to assess whether the invention satisfies the requirements of PCT Article 33(3). The present application does not appear to meet the requirements of PCT Article 33(2) because the subject matter of the claims is not novel. Claim 9 and pages 49-50 of the description of document D1 (WO 99/07692 A) concern, inter alia, a method for producing epothilone derivatives from the fragments A+B = A-B and A-B+C = A-B-C, wherein all three fragments structurally overlap with the fragments A, B and C claimed in the present application. The formula AB in claim 9 of document D1 therefore appears to be prejudicial to the novelty of the present claim 5. The method of claim 9 of document D1 likewise appears to be prejudicial to the novelty of the present claims 1-4. In particular, in the C fragment, U=C-R appears to overlap with G in document D1, and in fragment AB, CH-CH as opposed to D-E in AB of document D1 does not lead to a novel selection, since D-E form a unit, that is to say,

International application No.
PCT/EP2004/006685

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

they cannot be selected independently of each other.

Consequently, this is considered no more than a selection from a list.

Document D1 is the closest prior art. It discloses the Production of epothilone derivatives from the fragments A+B = A-B and A-B + C = A-B-C. The problem to be solved by the present invention is understood to be that of providing an alternative method, for the production of epothilones. In the light of the experimental part, it can be assumed that this problem is solved in the application. However, insofar as the subject matter of the present application can be considered novel, the fragments A, B and C are similar to those of document D1 to such an extent that the solution is obvious to a person skilled in the art. The problem to be solved by the present application must therefore considered that of making available an alternative method having unexpected or surprising properties with respect to the closest prior art document (D1). Without comparative test results or other arguments demonstrating the patentability of the invention it is not possible to assess whether the invention satisfies the requirements of PCT Article 33(3).

Lao, MariaLouisa

From:

DiNatale, John

Sent:

Thursday, October 11, 2007 4:01 PM

To:

Lao, MariaLouisa

Subject:

10/563058

Examiner Lao,

Your search results for serial number 10/563058 are complete and have been submitted to SCORE for posting. Routinely these results will be posted as early as <u>tomorrow</u>. Please see the instructions at the bottom of this email for retrieving search results <u>from eDan 2.2.1</u>.

**Search-specific notes:

The search results are located in 2 RTF files.

The organization of the search results within the RTF file called 20071011-10563058-str<u>1</u>.rtf is sequential, divided by page breaks:

- 1) author search
- 2) Claim 1 reaction search,
- 3) Claim 4 reaction search, and
- 4) search history.

The organization of the search results within the RTF file called 20071011-10563058-str2.rtf is sequential, divided by page breaks:

1) Claim 5 structure search

and

2) search history.

It may be helpful to save this memo as an index to the search results.

Please contact me if you have any questions.

Thank you, John DiNatale X2-2557

To access your search results via eDAN:

- 1) Enter Application number
- 2) Click on Supplemental Content Tab
- 3) <u>STN results</u> (structure and text searches) are under **Other Content** (click on version listed). <u>ABSS Sequence</u> results are under the **Search Results** (click on version listed).

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-3/B1 OR 220774-19-6/B1 OR 220774-20-9/B1 OR 220774-21-0/B1 OR 220774-22-1/B1 OR 220774-23-2/B1 OR 220774-59-4/B1 OR 220774-59-4/B1 OR 220774-60-7/B1 OR 220774-61-9/B1 OR 220774-62-9/B1 OR 220774-62-9/B1 OR 220775-76-8/B1 OR 220777-76-9/B1 OR 220775-76-9/B1 OR 220777-77-3/B1 OR 220775-76-9/B1 OR 220777-77-3/B1 OR 220777-77-1/B1 OR 220777-77-3/B1 OR 301154-55-4/B1 OR 301154-56-5/B1 OR 301154-59-7/B1 OR 301154-59-9/B1 OR 301154-59-7/B1 OR 821203-01-6/B1 OR 821203-01-7/B1 OR 821203-01-7/B1 OR 821203-01-7/B1 OR 821203-01-7/B1 OR 821203-01-7/B1 OR 821203-01-7/B1 OR 821203-01-6/B1 OR 821203-01-9/4/B1 OR 821203-01-9/4/B1 OR 821203-10-9/4/B1 OR 8 323203-14-1/BI OR 823203-15-2/BI OR 823203-16-3/BI OR 823203-17-4/BI OR 823203-18-5/BI OR 823203-10-4/BI OR 823203-18-5/BI OR 823203-18-5/BI OR 823203-23-2/BI OR 823203-24-3/BI OR 823203-25-4/BI OR 823203-27 -7/BI OR 823203-11-8/BI OR 823203-12-9/BI OR 823203-13-0/BI OR "131:31829"/AN OR "131:351125"/AN OR "132:49932"/AN OR "1197:206419"/AN OR "1997:206419"/AN OR "1997:490309"/AN OR "1997:665094"/AN OR "1997:787450"/AN OR "1998:377644764"/AN OR "1999:3772644"/AN OR "1999:37764474"/AN OR "1999:44724"/AN OR "1999:606636"/AN OR "1999:60636"/AN OR 'CASREACT' ENTERED AT 12:00:01 ON 11 OCT 2007 11 SEA ABB=ON PLU=ON ("126:21010"/AN OR "127:108793"/AN OR "127:293040"/AN OR "128:101936"/AN OR "129:199151"/AN OR "131:199535"/AN OR "131:286299"/AN OR "131:31819"/AN OR 'REGISTRY' ENTERED AT 11:54:40 ON 11 OCT 2007 E EPOTHILONE C/CN ENTERED AT 11:56:56 ON 11 OCT 2007 SN 10/563058 Page 169 of 172 STIC STN SEARCH RESULTS 'CAPLUS' ENTERED AT 11:50:53 ON 11 OCT 2007 1 SEA ABB=ON PLU=ON L67 AND L65 D SCA 'CAPLUS' ENTERED AT 11:58:45 ON 11 OCT 2007 11 SEA ABB=ON PLU=ON L45 AND PY<2000 1 SEA ABB=ON PLU=ON EPOTHILONE C/CN EPOTHILONE D/CN L42 (L) L71 L42 (L) L72 (L73 OR L74) L75 NOT L60 (L) 1/NS (L) 2/NS L78 AND L43 L79 OR L52 AND L73 AND L74 OR L79 O SEA ABB=ON PLU=ON L66 AND L39 D SCA NOT L63 143 152 152 161 161 1 SEA ABB-ON PLU-ON P.LU=0N PIU-ON PIU-ON NO-014 PLU=ON PLU-ON NO=014 PLU-ON D RN L67 1-2 7 SEA ABB-ON 7 SEA ABB-ON 14 SEA ABB-ON SEA ABB-ON SEA ABB-ON 21 SEA ABB-ON 14 SEA ABB-ON 13 SEA ABB=ON SEA ABB=ON SEA ABB=ON ABB=ON ABB=ON D FHIT SEL AN -6/BI) SCA ş CASREACT' SEA SEA SEA SEA Ω FILE FILE FILE FILE FILE

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OR "1999;372044"/AN OR "1999;383492"/AN OR "1999;444724"/AN OR
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D IBIB ABS LIOO 1-24
D DIBIB ABS LIOO 8-24
24 SEA ABB-GN PLU-6N L91 AND L92 AND L93 AND L94
D COST FULL
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21 SEA ABB=ON PLU=ON L45 AND PY<2001
SEL AN
AT 12:09:08 ON 11 OCT 2007
                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        FILE 'CAPLUS' ENTERED AT 12:11:29 ON 11 OCT 2007
                                                                                                                                                                             AND (1.92 OR
AND (1.93 OR
                              KLAR U?/AU
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STIC STN SEARCH RESULTS

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L43 (L) 4/NS L43 (L) 5/NS L85 NOT L88

PLU=ON PLU=ON PLU-ON

37 SEA ABB=ON 31 SEA ABB=ON 21 SEA ABB=ON 28 SEA ABB=ON

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"1999; 606636"/AN OR "1999:819379"/AN OR "2000:514132"/AN OR "2000:52387"/AN OR "2000:55974"/AN OR "2000:559403"/AN OR "2000:579403"/AN OR "2000:701228"/AN OR "2000:733774"/AN OR "2000:64216"/AN OR "2000:653645"/AN OR "2001:843887"/AN OR "2000:64216"/AN OR "2001:843887"/AN OR "2000:64216"/AN OR "2001:843887"/AN OR "2000:642887"/AN OR "2001:643887"/AN OR "2001:6438 D STAT QUE L109 D IBIB ABS FHIT L109 1-7 7 SEA ABB=ON F 7 SEA ABB=ON F

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